OFFICE OF INSPECTOR GENERAL

SPECIAL ADVISORY BULLETIN

OFFERING GIFTS AND OTHER INDUCEMENTS TO BENEFICIARIES

August 2002

Introduction

Under section 1128A(a)(5) of the Social Security Act (the Act), enacted as part of Health Insurance Portability and Accountability Act of 1996 (HIPAA), a person who offers or transfers to a Medicare or Medicaid beneficiary any remuneration that the person knows or should know is likely to influence the beneficiary's selection of a particular provider, practitioner, or supplier of Medicare or Medicaid payable items or services may be liable for civil money penalties (CMPs) of up to $10,000 for each wrongful act. For purposes of section 1128A(a)(5) of the Act, the statute defines "remuneration" to include, without limitation, waivers of copayments and deductible amounts (or any part thereof) and transfers of items or services for free or for other than fair market value. (See section 1128A(i)(6) of the Act.) The statute and implementing regulations contain a limited number of exceptions. (See section 1128A(i)(6) of the Act; 42 CFR 1003.101.)

Offering valuable gifts to beneficiaries to influence their choice of a Medicare or Medicaid provider[1] raises quality and cost concerns. Providers may have an economic incentive to offset the additional costs attributable to the giveaway by providing unnecessary services or by substituting cheaper or lower quality services. The use of giveaways to attract business also favors large providers with greater financial resources for such activities, disadvantaging smaller providers and businesses.

The Office of Inspector General (OIG) is responsible for enforcing section 1128A(a)(5) through administrative remedies. Given the broad language of the prohibition and the number of marketing practices potentially affected, this Bulletin is intended to alert the health care industry as to the scope of acceptable practices. To that end, this Bulletin

[1]For convenience, in this Special Advisory Bulletin, the term "provider" includes practitioners and suppliers, as defined in 42 CFR 400.202.

provides bright-line guidance that will protect the Medicare and Medicaid programs, encourage compliance, and level the playing field among providers. In particular, the OIG will apply the prohibition according to the following principles:

- First, the OIG has interpreted the prohibition to permit Medicare or Medicaid providers to offer beneficiaries inexpensive gifts (other than cash or cash equivalents) or services without violating the statute. For enforcement purposes, inexpensive gifts or services are those that have a retail value of no more than $10 individually, and no more than $50 in the aggregate annually per patient.

- Second, providers may offer beneficiaries more expensive items or services that fit within one of the five statutory exceptions: waivers of cost-sharing amounts based on financial need; properly disclosed copayment differentials in health plans; incentives to promote the delivery of certain preventive care services; any practice permitted under the federal anti-kickback statute pursuant to 42 CFR 1001.952; or waivers of hospital outpatient copayments in excess of the minimum copayment amounts.

- Third, the OIG is considering several additional regulatory exceptions. The OIG may solicit public comments on additional exceptions for complimentary local transportation and for free goods in connection with participation in certain clinical studies.

- Fourth, the OIG will continue to entertain requests for advisory opinions related to the prohibition on inducements to beneficiaries. However, as discussed below, given the difficulty in drawing principled distinctions between categories of beneficiaries or types of inducements, favorable opinions have been, and are expected to be, limited to situations involving conduct that is very close to an existing statutory or regulatory exception.

In sum, unless a provider's practices fit within an exception (as implemented by regulations) or are the subject of a favorable advisory opinion covering a provider's own activity, any gifts or free services to beneficiaries should not exceed the $10 per item and $50 annual limits.[2]

In addition, valuable services or other remuneration can be furnished to financially needy beneficiaries by an independent entity, such as a patient advocacy group, even if the benefits are funded by providers, so long as the independent entity makes an independent determination of need and the beneficiary's receipt of the remuneration does not depend, directly or indirectly, on the beneficiary's use of any particular provider. An example of

[2]The OIG will review these limits periodically and may adjust them for inflation if appropriate.

such an arrangement is the American Kidney Fund's program to assist needy patients with end stage renal disease with funds donated by dialysis providers, including paying for their supplemental medical insurance premiums. (See, e.g., OIG Advisory Opinion No. 97-1 and No. 02-1.)

Elements of the Prohibition

Remuneration. Section 1128A(a)(5) of the Act prohibits the offering or transfer of "remuneration". The term "remuneration" has a well-established meaning in the context of various health care fraud and abuse statutes. Generally, it has been interpreted broadly to include "anything of value." The definition of "remuneration" for purposes of section 1128A(a)(5) – which includes waivers of coinsurance and deductible amounts, and transfers of items or services for free or for other than fair market value – affirms this broad reading. (See section 1128A(i)(6).) The use of the term "remuneration" implicitly recognizes that virtually any good or service has a monetary value.[3]

The definition of "remuneration" in section 1128A(i)(6) contains five specific exceptions:

- Non-routine, unadvertised waivers of copayments or deductible amounts based on individualized determinations of financial need or exhaustion of reasonable collection efforts. Paying the premiums for a beneficiary's Medicare Part B or supplemental insurance is not protected by this exception.

- Properly disclosed differentials in a health insurance plan's copayments or deductibles. This exception covers incentives that are part of a health plan design, such as lower plan copayments for using preferred providers, mail order pharmacies, or generic drugs. Waivers of Medicare or Medicaid copayments are not protected by this exception.

- Incentives to promote the delivery of preventive care. Preventive care is defined in 42 CFR 1003.101 to mean items and services that (i) are covered by Medicare or Medicaid and (ii) are either pre-natal or post-natal well-baby services or are services described in the Guide to Clinical Preventive Services published by the U.S. Preventive Services Task Force (available online at http://odphp.osphs.dhhs.gov/pubs/guidecps). Such incentives may not be in the form of cash or cash equivalents and may not be disproportionate to the value of the preventive care provided. (See 42 CFR 1003.101; 65 FR 24400 and 24409.)

[3] Some services, such as companionship provided by volunteers, have psychological, rather than monetary value. (See, e.g., OIG Advisory Opinion No. 00-3.)

- Any practice permitted under an anti-kickback statute safe harbor at 42 CFR 1001.952.[4]

- Waivers of copayment amounts in excess of the minimum copayment amounts under the Medicare hospital outpatient fee schedule.

(See section 1128A(i)(6) of the Act; 42 CFR 1003.101.)

In addition, in the Conference Committee report accompanying the enactment of section 1128A(a)(5), Congress expressed its intent that inexpensive gifts of nominal value be permitted. (See Joint Explanatory Statement of the Committee of Conference, section 231 of HIPAA, Public Law 104-191.) Accordingly, the OIG interprets the prohibition to exclude offers of inexpensive items or services, and no specific exception for such items or services is required. (See 65 FR 24400 and 24410.) The OIG has interpreted inexpensive to mean a retail value of no more than $10 per item or $50 in the aggregate per patient on an annual basis. Id. at 24411.

Inducement. Section 1128A(a)(5) of the Act bars the offering of remuneration to Medicare or Medicaid beneficiaries where the person offering the remuneration knows or should know that the remuneration is likely to influence the beneficiary to order or receive items or services from a particular provider. The "should know" standard is met if a provider acts with deliberate ignorance or reckless disregard. No proof of specific intent is required. (See 42 CFR 1003.101.)

The "inducement" element of the offense is met by any offer of valuable (i.e., not inexpensive) goods and services as part of a marketing or promotional activity, regardless of whether the marketing or promotional activity is active or passive. For example, even if a provider does not directly advertise or promote the availability of a benefit to beneficiaries, there may be indirect marketing or promotional efforts or informal channels of information dissemination, such as "word of mouth" promotion by practitioners or patient support groups. In addition, the OIG considers the provision of free goods or services to existing customers who have an ongoing relationship with a provider likely to influence those customers' future purchases.

Beneficiaries. Section 1128A(a)(5) of the Act bars inducements offered to Medicare and Medicaid beneficiaries, regardless of the beneficiary's medical condition. The OIG is aware that some specialty providers offer valuable gifts to beneficiaries with specific chronic conditions. In many cases, these complimentary goods or services have therapeutic, as well as financial, benefits for patients. While the OIG is mindful of the

[4] For example, anti-kickback statute safe harbors exist for warranties; discounts; employee compensation; waivers of certain beneficiary coinsurance and deductible amounts; and increased coverage, reduced cost-sharing amounts, or reduced premium amounts offered by health plans. See 42 CFR 1001.952(g), (h), (i), and (k).

hardships that chronic medical conditions can cause for beneficiaries, there is no meaningful basis under the statute for exempting valuable gifts based on a beneficiary's medical condition or the condition's severity. Moreover, providers have a greater incentive to offer gifts to chronically ill beneficiaries who are likely to generate substantially more business than other beneficiaries.

Similarly, there is no meaningful statutory basis for a broad exemption based on the financial need of a category of patients. The statute specifically applies the prohibition to the Medicaid program – a program that is available only to financially needy persons. The inclusion of Medicaid within the prohibition demonstrates Congress' conclusion that categorical financial need is not a sufficient basis for permitting valuable gifts. This conclusion is supported by the statute's specific exception for non-routine waivers of copayments and deductibles based on individual financial need. If Congress intended a broad exception for financially needy persons, it is unlikely that it would have expressly included the Medicaid program within the prohibition and then created such a narrow exception.

Provider, Practitioner, or Supplier. Section 1128A(a)(5) of the Act applies to incentives to select particular providers, practitioners, or suppliers. As noted in the regulations, the OIG has interpreted this element to exclude health plans that offer incentives to Medicare and Medicaid beneficiaries to enroll in a plan. (See 65 FR 24400 and 24407.) However, incentives provided to influence an already enrolled beneficiary to select a particular provider, practitioner, or supplier within the plan are subject to the statutory proscription (other than copayment differentials that are part of a health plan design). Id. In addition, the OIG does not believe that drug manufacturers are "providers, practitioners, or suppliers" for the limited purposes of section 1128A(a)(5), unless the drug manufacturers also own or operate, directly or indirectly, pharmacies, pharmacy benefits management companies, or other entities that file claims for payment under the Medicare or Medicaid programs.

Additional Regulatory Considerations

Congress has authorized the OIG to create regulatory exceptions to section 1128A(a)(5) of the Act and to issue advisory opinions to protect acceptable arrangements. (See sections 1128A(i)(6)(B) and 1128D(b)(2)(A) of the Act.) While the OIG has considered numerous arrangements involving the provision of various free goods and services to beneficiaries, for the following reasons the OIG has concluded that any additional exceptions will likely be few in number and narrow in scope:

- Any exception will create the activity that the statute prohibits – namely, competing for business by giving remuneration to Medicare and Medicaid beneficiaries. Moreover, competition will not only result in providers matching a competitor's offer, but inevitably will trigger ever more valuable

offers.

- Since virtually all free goods and services have a corresponding monetary value, there is no principled basis under the statute for distinguishing between the kinds of goods or services offered or the types of beneficiaries to whom the goods or services are offered. Attempting to draw such distinctions would necessarily result in arbitrary standards and would undermine the entire prohibition. Congress has provided no further statutory guidance on the bases for distinguishing and evaluating potential exceptions.

Despite these serious concerns, the OIG is considering soliciting public comment on the possibility of regulatory "safe harbor" exceptions under section 1128A(a)(5) for two kinds of arrangements:

- **Complimentary local transportation.** The OIG is considering proposing a new exception for complimentary local transportation offered to beneficiaries residing in the provider's primary catchment area. The proposal would permit some complimentary local transportation of greater than nominal value. However, the exception would not cover luxury or specialized transportation, including limousines or ambulances (but would permit vans specially outfitted to transport wheelchairs). The proposed exception may include transportation to the office or facility of a provider other than the donor; however, such arrangements may implicate the anti-kickback statute insofar as they confer a benefit on a provider that is a potential referral source for the party providing the transportation.

- **Government-sponsored clinical trials.** The OIG may propose a new exception for free goods and services (possibly including waivers of copayments) in connection with certain clinical trials that are principally sponsored by the National Institutes of Health or another component of the Department of Health and Human Services.

The OIG is reviewing its pending proposal (65 FR 25460) to permit certain dialysis providers to purchase Medicare supplemental insurance for financially needy persons in the light of the principles established in this Bulletin.

While the OIG does not expect at this time to propose any additional regulatory exceptions related to unadvertised waivers of copayments and deductibles, the OIG recognizes that such waivers occur in a wide variety of circumstances, some of which do not present a significant risk of fraud and abuse. The OIG encourages the industry to bring these situations to our attention through the advisory opinion process. Instructions for requesting an OIG advisory opinion are available on the OIG website at http://oig.hhs.gov/fraud/advisoryopinions.html

Finally, the OIG reiterates that nothing in section 1128A(a)(5) prevents an independent entity, such as a patient advocacy group, from providing free or other valuable services or remuneration to financially needy beneficiaries, even if the benefits are funded by providers, so long as the independent entity makes an independent determination of need and the beneficiary's receipt of the remuneration does not depend, directly or indirectly, on the beneficiary's use of any particular provider. The OIG has approved several such arrangements through the advisory opinion process, including the American Kidney Fund's program to assist needy patients with end stage renal disease with funds donated by dialysis providers. (See, e.g., OIG Advisory Opinion No. 97-1 and No. 02-1.)

Conclusion

Congress has broadly prohibited offering remuneration to Medicare and Medicaid beneficiaries, subject to limited, well-defined exceptions. To the extent that providers have programs in place that do not meet any exception, the OIG, in exercising its enforcement discretion, will take into consideration whether the providers terminate prohibited programs expeditiously following publication of this Bulletin.

The Office of Inspector General (OIG) was established at the Department of Health and Human Services by Congress in 1976 to identify and eliminate fraud, abuse, and waste in the Department's programs and to promote efficiency and economy in departmental operations. The OIG carries out this mission through a nationwide program of audits, investigations, and inspections.

The Fraud and Abuse Control Program, established by the Health Insurance Portability and Accountability Act of 1996 (HIPAA), authorized the OIG to provide guidance to the health care industry to prevent fraud and abuse and to promote the highest level of ethical and lawful conduct. To further these goals, the OIG issues Special Advisory Bulletins about industry practices or arrangements that potentially implicate the fraud and abuse authorities subject to enforcement by the OIG.

FDA NEWS RELEASE

FDA approves new treatments for heart disease caused by a serious rare disease, transthyretin mediated amyloidosis

For Immediate Release:

May 06, 2019

On May 3, the U.S. Food and Drug Administration approved Vyndaqel (tafamidis meglumine) and Vyndamax (tafamidis) capsules for the treatment of the heart disease (cardiomyopathy) caused by transthyretin mediated amyloidosis (ATTR-CM) in adults. These are the first FDA-approved treatments for ATTR-CM. Vyndaqel and Vyndamax have the same active moiety, tafamidis, but they are not substitutable on a milligram to milligram basis and their recommended doses differ.

“Transthyretin-mediated amyloidosis is a rare, debilitating and often fatal disease,” said Norman Stockbridge, M.D., Ph.D., director of the Division of Cardiovascular and Renal Drugs in the FDA’s Center for Drug Evaluation and Research. “The treatments we’re approving today are an important advancement in the treatment of the cardiomyopathy caused by transthyretin-mediated amyloidosis.”

ATTR is caused by the buildup of abnormal deposits of specific proteins known as amyloid in the body's organs and tissues, interfering with their normal functioning. These protein deposits most frequently occur in the heart and the peripheral nervous system. Heart involvement can result in shortness of breath, fatigue, heart failure, loss of consciousness, abnormal heart rhythms and death. Involvement of the peripheral nervous system can result in a loss of sensation, pain, or immobility in the arms, legs, hands and feet. Amyloid deposits can also affect the kidneys, eyes, gastrointestinal tract and central nervous system.

The efficacy of Vyndaqel and Vyndamax in treating ATTR-CM was shown in a clinical trial of 441 patients randomized to receive Vyndaqel or a placebo. After an average of 30 months, the survival rate was higher in the Vyndaqel group than in the placebo group. Vyndaqel was also shown to reduce the number of hospitalizations for cardiovascular problems.

The number of patients in clinical studies was small, but no drug-associated side effects have been identified. Tafamidis may cause fetal harm when administered to a pregnant woman. Women taking Vyndaqel or Vyndamax should discuss pregnancy planning and prevention with their health care professional.

The FDA granted Vyndaqel Fast Track (/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track), Priority Review (/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review) and Breakthrough Therapy (/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy) designations. Vyndaqel and Vyndamax each received Orphan Drug (/industry/developing-products-rare-diseases-conditions/designating-orphan-product-drugs-and-biological-products) designation, which provides incentives to assist and encourage the development of drugs for rare diseases.

Approval of Vyndaqel and Vyndamax were granted to FoldRx, a subsidiary of Pfizer.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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Consumer:

888-INFO-FDA

More Press Announcements (/news-events/newsroom/press-announcements)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VYNDAQEL and VYNDAMAX safely and effectively. See full prescribing information for VYNDAQEL and VYNDAMAX.

VYNDAQEL® (tafamidis meglumine) capsules, for oral administration
Initial U.S. Approval: 2019

VYNDAMAX™ (tafamidis) capsules, for oral administration
Initial U.S. Approval: 2019

---------- INDICATIONS AND USAGE----------
VYNDAQEL and VYNDAMAX are transthyretin stabilizers indicated for the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization. (1)

----------DOSAGE AND ADMINISTRATION----------
The recommended dosage is either:
- VYNDAQEL 80 mg orally once daily, or
- VYNDAMAX 61 mg orally once daily (2.1)
- VYNDAMAX and VYNDAQEL are not substitutable on a per mg basis. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------
Capsules: Tafamidis meglumine 20 mg and tafamidis 61 mg. (3)

---------- CONTRAINDICATIONS ----------
None. (4)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- USE IN SPECIFIC POPULATIONS ----------
- Pregnancy: Based on animal studies, may cause fetal harm. (8.1)
- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 05/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

VYNDAQEL and VYNDAMAX are indicated for the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage is either VYNDAQEL 80 mg (four 20-mg tafamidis meglumine capsules) orally once daily or VYNDAMAX 61 mg (one 61-mg tafamidis capsule) orally once daily.

VYNDAMAX and VYNDAQEL are not substitutable on a per mg basis *[see Clinical Pharmacology (12.3)]*.

2.2 Administration Instructions

The capsules should be swallowed whole and not crushed or cut.

If a dose is missed, instruct patients to take the dose as soon as remembered or to skip the missed dose and take the next dose at the regularly scheduled time. Do not double the dose.

3. DOSAGE FORMS AND STRENGTHS

VYNDAQEL is available as:

- tafamidis meglumine 20 mg: yellow, opaque, oblong capsule, printed with “VYN 20” in red.

VYNDAMAX is available as:

- tafamidis 61 mg: reddish brown, opaque, oblong capsule, printed with “VYN 61” in white.

4. CONTRAINDICATIONS

None.

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data reflect exposure of 377 ATTR-CM patients to 20 mg or 80 mg (administered as four 20-mg capsules) of VYNDAQEL administered daily for an average of 24.5 months (ranging from 1 day to 111 months).

Adverse events were assessed from ATTR-CM clinical trials with VYNDAQEL, primarily a 30-month placebo-controlled trial *[see Clinical Studies (14)]*. The frequency of adverse events in patients treated with VYNDAQEL 20 mg (n=88) or 80 mg (n=176; administered as four 20-mg capsules) was similar to that with placebo (n=177).

In the 30-month placebo-controlled trial, similar proportions of VYNDAQEL-treated patients and placebo-treated patients discontinued the study drug because of an adverse event: 12 (7%), 5 (6%), and 11 (6%) from the VYNDAQEL 80-mg, VYNDAQEL 20-mg, and placebo groups, respectively.

7. DRUG INTERACTIONS

7.1 BCRP Substrates

Tafamidis inhibits breast cancer resistant protein (BCRP) in vitro and may increase exposure of substrates of this transporter (e.g., methotrexate, rosuvastatin, imatinib) following VYNDAQEL 80 mg or VYNDAMAX 61 mg. Dose adjustment may be needed for these substrates.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies, VYNDAQEL and VYNDAMAX may cause fetal harm when administered to a pregnant woman. However, limited available human data with VYNDAQEL use in pregnant women (at a dose of 20 mg per day) have not identified any drug-associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproductive studies, oral administration of tafamidis meglumine to pregnant rabbits during organogenesis resulted in adverse effects on development (embryofetal mortality, fetal body weight reduction and fetal malformation) at a dosage providing approximately 9 times the human exposure (AUC) at the maximum recommended human dose (MRHD) of VYNDAQEL (80 mg), and increased incidence of fetal skeletal variation at a dosage providing equivalent human exposure (AUC) at the MRHD. Postnatal mortality, growth retardation, and impaired learning and memory were observed in offspring of pregnant rats administered tafamidis meglumine during gestation and lactation at a dosage approximately 2 times the MRHD based on body surface area (mg/m^2) *(see Data)*. Advise pregnant women of the potential risk to a fetus. Report pregnancies to the Pfizer reporting line at 1-800-438-1985.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In pregnant rats, oral administration of tafamidis meglumine (0, 15, 30, and 45 mg/kg/day) throughout organogenesis resulted in decreased fetal body weights at ≥30 mg/kg/day (approximately 10 times the human exposure at the MRHD based on AUC). The no-observed-adverse-effect-level (NOAEL) for embryofetal development in rats was 15 mg/kg/day (approximately 7 times the human exposure at the MRHD based on AUC).

In pregnant rabbits, oral administration of tafamidis meglumine (0, 0.5, 2, and 8 mg/kg/day) throughout organogenesis resulted in increased embryofetal mortality, reduced fetal body weights, and an increased incidence of fetal malformations at 8 mg/kg/day (approximately 9 times the human exposure at the MRHD based on AUC), which was also maternally toxic. Increased incidences of fetal skeletal variations were observed at doses ≥0.5 mg/kg/day (approximately equivalent to the human exposure at the MRHD based on AUC).

In the pre- and postnatal study, pregnant rats received oral administration of tafamidis meglumine at doses of 0, 5, 15, or 30 mg/kg/day throughout pregnancy and lactation (Gestation Day 7 to Lactation Day 20). Decreased survival and body weights, delayed male sexual maturation and neurobehavioral effects (learning and memory impairment) were observed in the offspring of dams treated at 15 mg/kg/day (approximately 2 times the MRHD on a mg/m^2 basis). The NOAEL for pre- and postnatal development in rats was 5 mg/kg/day (approximately equivalent to the MRHD on a mg/m^2 basis).

8.2 Lactation

Risk Summary

There are no available data on the presence of tafamidis in human milk, the effect on the breastfed infant, or the effect on milk production. Tafamidis is present in rat milk *(see Data)*. When a drug is present in animal milk, it is likely the drug will be present in human milk. Based on findings from animal studies which suggest the potential for serious adverse reactions in the breastfed infant, advise patients that breastfeeding is not recommended during treatment with VYNDAQEL or VYNDAMAX.

Data

Pregnant and lactating female rats were administered repeated daily oral doses of tafamidis meglumine (15 mg/kg/day) followed by a single oral gavage dose of ^{14}C-tafamidis meglumine on Lactation Day 4 or 12. Radioactivity was observed in milk by 1 hour post-dose and increased thereafter. The ratio of the highest radioactivity associated with ^{14}C tafamidis meglumine in milk (8 hours post-dose) vs. plasma (1 hour post-dose) was approximately 1.6 on Day 12, indicating tafamidis meglumine is transferred to milk after oral administration.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Based on findings from animal studies, VYNDAQEL and VYNDAMAX may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Consider pregnancy planning and prevention for females of reproductive potential.

8.4 Pediatric Use

The safety and effectiveness of VYNDAQEL and VYNDAMAX have not been established in pediatric patients.

8.5 Geriatric Use

No dosage adjustment is required for elderly patients (≥65 years) *[see Clinical Pharmacology (12.3)]*. Of the total number of patients in the clinical study (n=441), 90.5% were 65 and over, with a median age of 75 years.

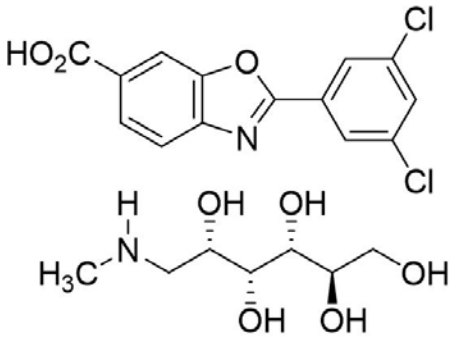
10. OVERDOSAGE

There is minimal clinical experience with overdose. During clinical trials, two patients accidentally ingested a single VYNDAQEL dose of 160 mg without adverse events. The highest dose of tafamidis meglumine given to healthy volunteers in a clinical trial was 480 mg as a single dose. There was one reported adverse event of mild hordeolum at this dose.

11. DESCRIPTION

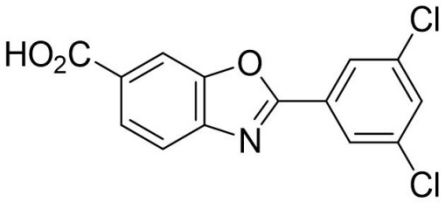
VYNDAQEL (tafamidis meglumine) and VYNDAMAX (tafamidis) contain tafamidis as the active moiety, which is a selective stabilizer of transthyretin.

The chemical name of tafamidis meglumine is 2-(3,5-dichlorophenyl)-1,3-benzoxazole-6-carboxylic acid mono (1-deoxy-1-methylamino-D-glucitol). The molecular formula is $C_{14}H_7Cl_2NO_3$ $C_7H_{17}NO_5$, and the molecular weight is 503.33 g/mol. The structural formula is:



Tafamidis meglumine 20-mg soft gelatin capsule for oral use contains a white to pink colored suspension of tafamidis meglumine 20 mg (equivalent to 12.2 mg of tafamidis free acid), and the following inactive ingredients: ammonium hydroxide 28%, brilliant blue FCF, carmine, ethyl alcohol, gelatin, glycerin, iron oxide (yellow), isopropyl alcohol, polyethylene glycol 400, polysorbate 80, polyvinyl acetate phthalate, propylene glycol, purified water, sorbitan monooleate, sorbitol, and titanium dioxide.

The chemical name of tafamidis is 2-(3,5-dichlorophenyl)-1,3-benzoxazole-6-carboxylic acid. The molecular formula is $C_{14}H_7Cl_2NO_3$, and the molecular weight is 308.12 g/mol. The structural formula is:



Tafamidis 61-mg soft gelatin capsule for oral use contains a white to pink colored suspension of tafamidis 61 mg and the following inactive ingredients: ammonium hydroxide 28%, butylated hydroxytoluene, ethyl alcohol, gelatin, glycerin, iron oxide (red), isopropyl alcohol, polyethylene glycol 400, polysorbate 20, povidone (K-value 90), polyvinyl acetate phthalate, propylene glycol, purified water, sorbitol, and titanium dioxide.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tafamidis is a selective stabilizer of TTR. Tafamidis binds to TTR at the thyroxine binding sites, stabilizing the tetramer and slowing dissociation into monomers, the rate-limiting step in the amyloidogenic process.

12.2 Pharmacodynamics

A proprietary TTR stabilization assay was utilized as a pharmacodynamic marker and assessed the stability of the TTR tetramer ex vivo. The TTR stabilization assay quantifies immunoturbidimetric measurement of the stable TTR tetramer in plasma pre- and post-treatment with 2-day in vitro denaturation with urea. Using this proprietary assay, a dose-dependent trend for greater TTR tetramer stabilization is observed for VYNDAQEL 80-mg compared to VYNDAQEL 20-mg. However, the clinical relevance of a higher TTR tetramer stabilization towards cardiovascular outcomes is not known.

VYNDAQEL stabilized both the wild type TTR tetramer and the tetramers of 14 TTR variants tested clinically after once-daily dosing. Tafamidis also stabilized the TTR tetramer for 25 variants tested ex vivo.

VYNDAQEL and VYNDAMAX may decrease serum concentrations of total thyroxine, without an accompanying change in thyroid stimulating hormone (TSH). This reduction in total thyroxine values is probably the result of reduced thyroxine binding to or displacement from transthyretin (TTR) due to the high binding affinity of tafamidis to the TTR thyroxine receptor. No corresponding clinical findings consistent with hypothyroidism have been observed.

Biomarkers associated with heart failure (NT-proBNP and Troponin I) favored VYNDAQEL over placebo.

Cardiac Electrophysiology
At approximately 2.2 times the steady state peak plasma concentration (C_{max}) at the recommended dose, tafamidis does not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

No clinically significant differences in steady state C_{max} and area under the plasma concentration over time curve (AUC) of tafamidis were observed for VYNDAMAX 61-mg capsule compared to VYNDAQEL administered as four 20-mg capsules.

Tafamidis exposure increases proportionally over single (up to 480 mg) or multiple (up to 80 mg) (1 to 6 times the approved recommended dosage) once daily dosing.

The apparent clearance were similar after single and repeated administration of VYNDAQEL 80 mg.

Absorption
Median tafamidis peak concentrations occurred within 4 hours following dosing.

Effect of Food
No clinically significant differences in the pharmacokinetics of tafamidis were observed following administration of a high fat, high calorie meal.

Distribution
The apparent steady state volume of distribution of tafamidis is approximately 18.5 liters. Plasma protein binding of tafamidis is >99% in vitro. Tafamidis primarily binds to TTR.

Elimination
The mean half-life of tafamidis is approximately 49 hours. The apparent oral clearance of tafamidis is 0.263 L/hr. The degree of drug accumulation at steady state after repeated tafamidis daily dosing is approximately 2.5-fold greater than that observed after a single dose.

Metabolism
The metabolism of tafamidis has not been fully characterized. However, glucuronidation has been observed.

Excretion
After a single oral dose of tafamidis meglumine 20 mg, approximately 59% of the dose was recovered in feces (mostly as the unchanged drug) and approximately 22% of the dose was recovered in urine (mostly as the glucuronide metabolite).

Specific Populations
No clinically significant differences in the pharmacokinetics of tafamidis were observed based on age, race/ethnicity (Caucasian and Japanese) or renal impairment.

Patients with Hepatic Impairment
Patients with moderate hepatic impairment (Child-Pugh Score of 7 to 9) had decreased systemic exposure (approximately 40%) and increased clearance (approximately 68%) of tafamidis compared to healthy subjects. As TTR levels are lower in subjects with moderate hepatic impairment than in healthy subjects, the exposure of tafamidis relative to the amount of TTR is sufficient to maintain stabilization of the TTR tetramer in these patients. No clinically significant differences in the pharmacokinetics of tafamidis were observed in patients with mild hepatic impairment (Child Pugh Score of 5 to 6) compared to healthy subjects. The effect of severe hepatic impairment on tafamidis is unknown.

Drug Interaction Studies
Clinical Studies
No clinically significant differences in the pharmacokinetics of midazolam (a CYP3A4 substrate) or on the formation of its active metabolite (1-hydroxymidazolam) were observed when a single 7.5-mg dose of midazolam was administered prior to and after a 14-day regimen of VYNDAQEL 20-mg once daily.

In Vitro Studies
Cytochrome P450 Enzymes: Tafamidis induces CYP2B6 and CYP3A4 and does not induce CYP1A2. Tafamidis does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5 or CYP2D6.

UDP glucuronosyltransferase (UGT): Tafamidis inhibits intestinal activities of UGT1A1 but neither induces nor inhibits other UDP glucuronosyltransferase (UGT) systemically.

Transporter Systems: Tafamidis inhibits breast cancer resistant protein (BCRP). In vitro studies and model predictions show that tafamidis has a low potential to inhibit organic anion transporters OAT1 and OAT3 at clinically relevant concentrations. Tafamidis did not show a potential to inhibit Multi-Drug Resistant Protein (MDR1) (also known as P-glycoprotein; P-gp), organic cation transporter OCT2, multidrug and toxin extrusion transporters MATE1 and MATE2K and, organic anion transporting polypeptide OATP1B1 and OATP1B3.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
There was no evidence of an increased incidence of neoplasia in the transgenic (Tg)-rasH2 mouse following repeated daily administration for 26 weeks at daily doses of 0, 10, 30 or 90 mg/kg. There was no evidence of increased incidence of neoplasia in a 2-year carcinogenicity study in rats at exposures up to 18 times the AUC at the MRHD.

Mutagenesis

There was no evidence of mutagenicity or clastogenicity in vitro, and an in vivo rat micronucleus study was negative.

Impairment of Fertility

There were no effects of tafamidis meglumine on fertility, reproductive performance, or mating behavior in the rat at any dose. Rats were dosed daily (0, 5, 15, and 30 mg/kg/day) prior to cohabitation (for at least 15 days for females and 28 days for males), throughout the cohabitation period to the day prior to termination of males and through to implantation of females (Gestation Day 7). No adverse effects were noted on male and female rats in toxicity, fertility, and mating behavior at any dose. The paternal and maternal no observed adverse effect level for reproductive toxicity of tafamidis meglumine is 30 mg/kg/day, approximately 4 times the MRHD on a mg/m^2 basis.

14. CLINICAL STUDIES

Efficacy was demonstrated in a multicenter, international, randomized, double-blind, placebo-controlled study in 441 patients with wild type or hereditary ATTR-CM (NCT01994889).

Patients were randomized in a 1:2:2 ratio to receive VYNDAQEL 20 mg (n=88), VYNDAQEL 80 mg (administered as four 20-mg VYNDAQEL capsules) (n=176), or matching placebo (n=177) once daily for 30 months, in addition to standard of care (e.g., diuretics). Treatment assignment was stratified by the presence or absence of a variant TTR genotype as well as baseline disease severity (NYHA Class). Transplant patients were excluded from this study. Table 1 describes the patient demographics and baseline characteristics.

Table 1: Patient Demographics and Baseline Characteristics

Characteristic	**Pooled Tafamidis N=264**	**Placebo N=177**
Age — years		
Mean (standard deviation)	74.5 (7.2)	74.1 (6.7)
Median (minimum, maximum)	75 (46, 88)	74 (51, 89)
Sex — number (%)		
Male	241 (91.3)	157 (88.7)
Female	23 (8.7)	20 (11.3)
TTR Genotype — number (%)		
ATTRm	63 (23.9)	43 (24.3)
ATTRwt	201 (76.1)	134 (75.7)
NYHA Class — number (%)		
NYHA Class I	24 (9.1)	13 (7.3)
NYHA Class II	162 (61.4)	101 (57.1)
NYHA Class III	78 (29.5)	63 (35.6)

Abbreviations: ATTRm = variant transthyretin amyloid, ATTRwt = wild type transthyretin amyloid

The primary analysis used a hierarchical combination applying the method of Finkelstein-Schoenfeld (F-S) to all-cause mortality and frequency of cardiovascular-related hospitalizations, which was defined as the number of times a subject was hospitalized (i.e., admitted to a hospital) for cardiovascular-related morbidity. The method compared each patient to every other patient within each stratum in a pair-wise manner that proceeded in a hierarchical fashion using all-cause mortality followed by frequency of cardiovascular-related hospitalizations when patients could not be differentiated based on mortality.

This analysis demonstrated a significant reduction (p=0.0006) in all-cause mortality and frequency of cardiovascular-related hospitalizations in the pooled VYNDAQEL 20-mg and 80-mg groups versus placebo (Table 2).

Table 2: Primary Analysis Using Finkelstein-Schoenfeld (F-S) Method of All-Cause Mortality and Frequency of Cardiovascular-Related Hospitalizations

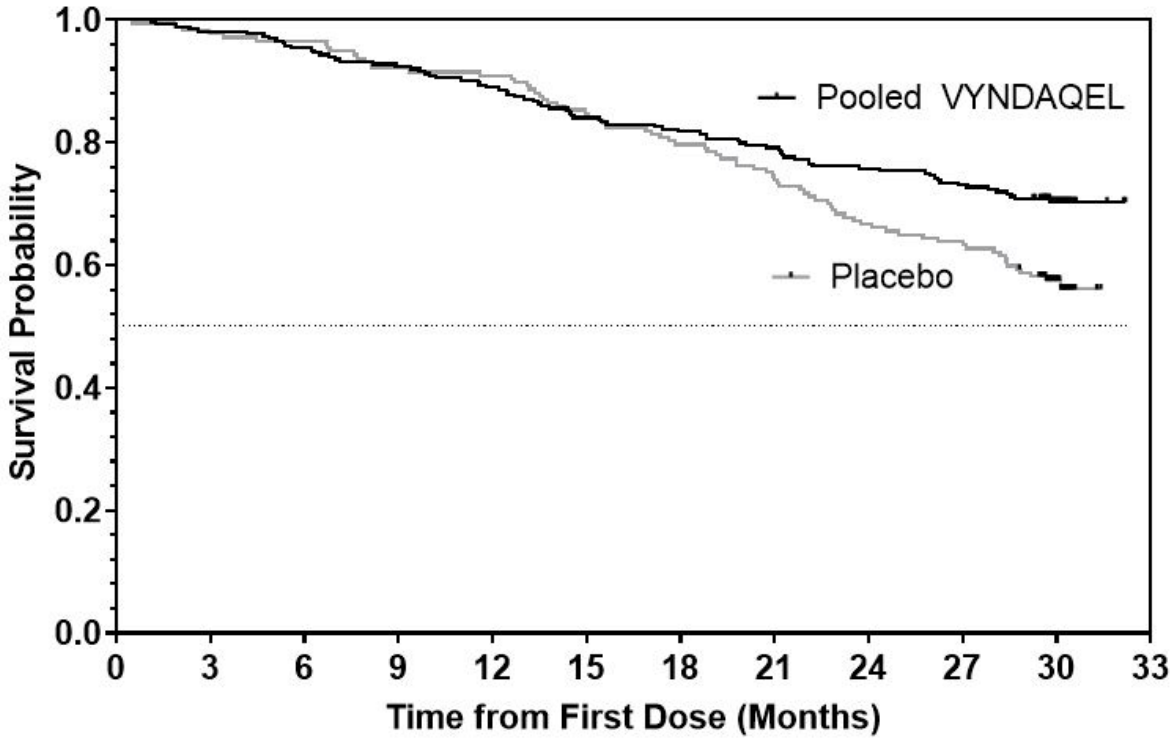
Primary Analysis	**Pooled VYNDAQEL N=264**	**Placebo N=177**
Number (%) of Subjects Alive* at Month 30	186 (70.5)	101 (57.1)
Mean Number of Cardiovascular-related Hospitalizations During 30 months (per patient per year) Among Those Alive at Month 30	0.297	0.455
p-value from F-S Method	0.0006	

* Heart transplantation and cardiac mechanical assist device implantation are considered indicators of approaching end stage. As such, these subjects are treated in the analysis as equivalent to death. Therefore, such subjects are not included in the count of "Number of Subjects Alive at Month 30" even if such subjects are alive based on 30 month vital status follow-up assessment.

Analysis of the individual components of the primary analysis (all-cause mortality and cardiovascular-related hospitalization) also demonstrated significant reductions for VYNDAQEL versus placebo.

The hazard ratio from the all-cause mortality Cox-proportional hazard model for pooled VYNDAQEL versus placebo was 0.70 (95% confidence interval [CI] 0.51, 0.96), indicating a 30% relative reduction in the risk of death relative to the placebo group (p=0.026). Approximately 80% of total deaths were cardiovascular-related in both treatment groups. A Kaplan-Meier plot of time to event all-cause mortality is presented in Figure 1.

Figure 1: All-Cause Mortality*



Subjects Remaining at Risk
(Cumulative events)

Pooled	264	259	252	244	235	222	216	209	200	193	99	0
VYNDAQEL	0	5	12	20	29	42	48	55	64	71	76	78
Placebo	177	173	171	163	161	150	141	131	118	113	51	0
	0	4	6	14	16	27	36	46	59	64	75	76

*Heart transplants and cardiac mechanical assist devices treated as death. Hazard ratio from Cox proportional hazards model with treatment, TTR genotype (variant and wild type), and NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III) as factors.

There were significantly fewer cardiovascular-related hospitalizations with VYNDAQEL compared with placebo with a reduction in risk of 32% corresponding to a Relative Risk Ratio of 0.68 (Table 3).

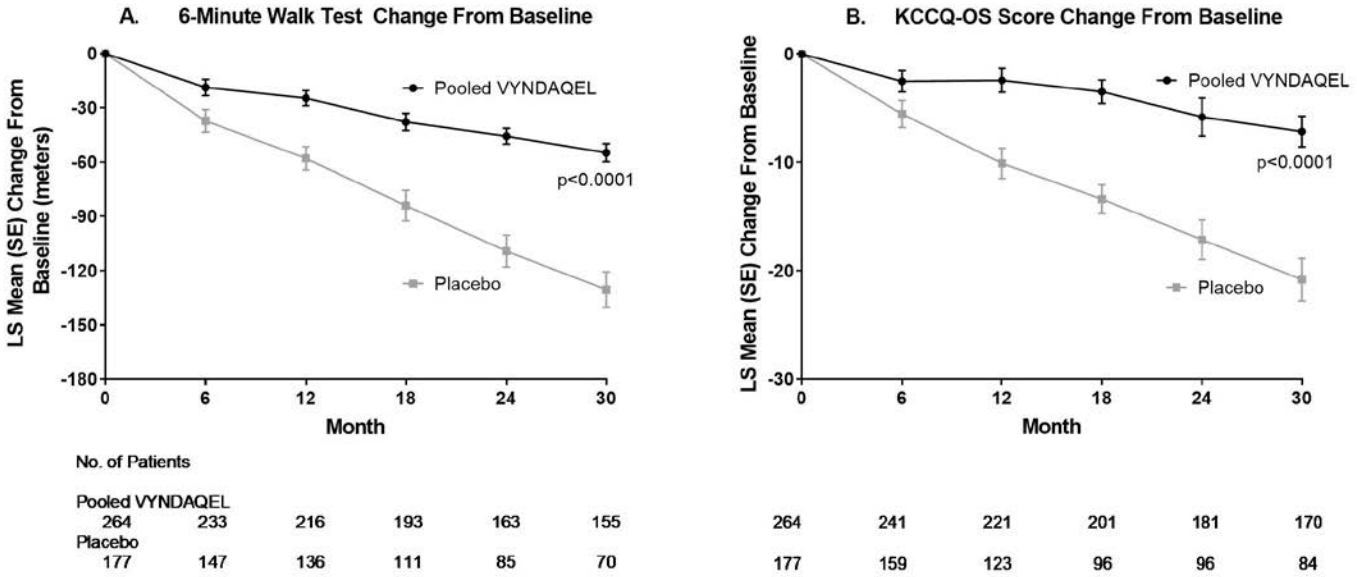
Table 3: Cardiovascular-Related Hospitalization Frequency

	Pooled VYNDAQEL N=264	**Placebo N=177**
Total (%) Number of Subjects with Cardiovascular-related Hospitalizations	138 (52.3)	107 (60.5)
Cardiovascular-related Hospitalizations per Year*	0.48	0.70
Pooled VYNDAQEL vs Placebo Treatment Difference (Relative Risk Ratio)*	0.68	
p-value*	<0.0001	

*This analysis was based on a Poisson regression model with treatment, TTR genotype (variant and wild type), New York Heart Association (NYHA). Baseline classification (NYHA Classes I and II combined and NYHA Class III), treatment-by-TTR genotype interaction, and treatment-by-NYHA baseline classification interaction terms as factors.

The treatment effects of VYNDAQEL on functional capacity and health status were assessed by the 6-Minute Walk Test (6MWT) and the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score, respectively. A significant treatment effect favoring VYNDAQEL was first observed at Month 6 and remained consistent through Month 30 on both 6MWT distance and KCCQ-OS score (Figure 2 and Table 4).

Figure 2: Change from Baseline to Month 30 in 6MWT Distance and KCCQ-OS Score



Panel A shows change from Baseline to Month 30 in pooled VYNDAQEL patients compared with placebo patients in 6MWT distance.
Panel B shows change from Baseline to Month 30 in pooled VYNDAQEL patients compared with placebo patients in KCCQ-OS score.

The Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score is composed of four domains including Total Symptoms (Symptom Frequency and Symptom Burden), Physical Limitation, Quality of Life, and Social Limitation. The Overall Summary score and domain scores range from 0 to 100, with higher scores representing better health status. All four domains favored pooled VYNDAQEL compared to placebo at Month 30, and demonstrated similar treatment effects to the KCCQ-OS score (Figure 2 and Table 4). The distribution for change from Baseline to Month 30 for KCCQ-OS (Figure 3) shows that the proportion of patients with worse KCCQ-OS scores was lower for the pooled VYNDAQEL-treated group compared to placebo, and the proportion with improved scores was higher (Figure 3).

Figure 3: Histogram of Change from Baseline to Month 30 in KCCQ-Overall Summary Score

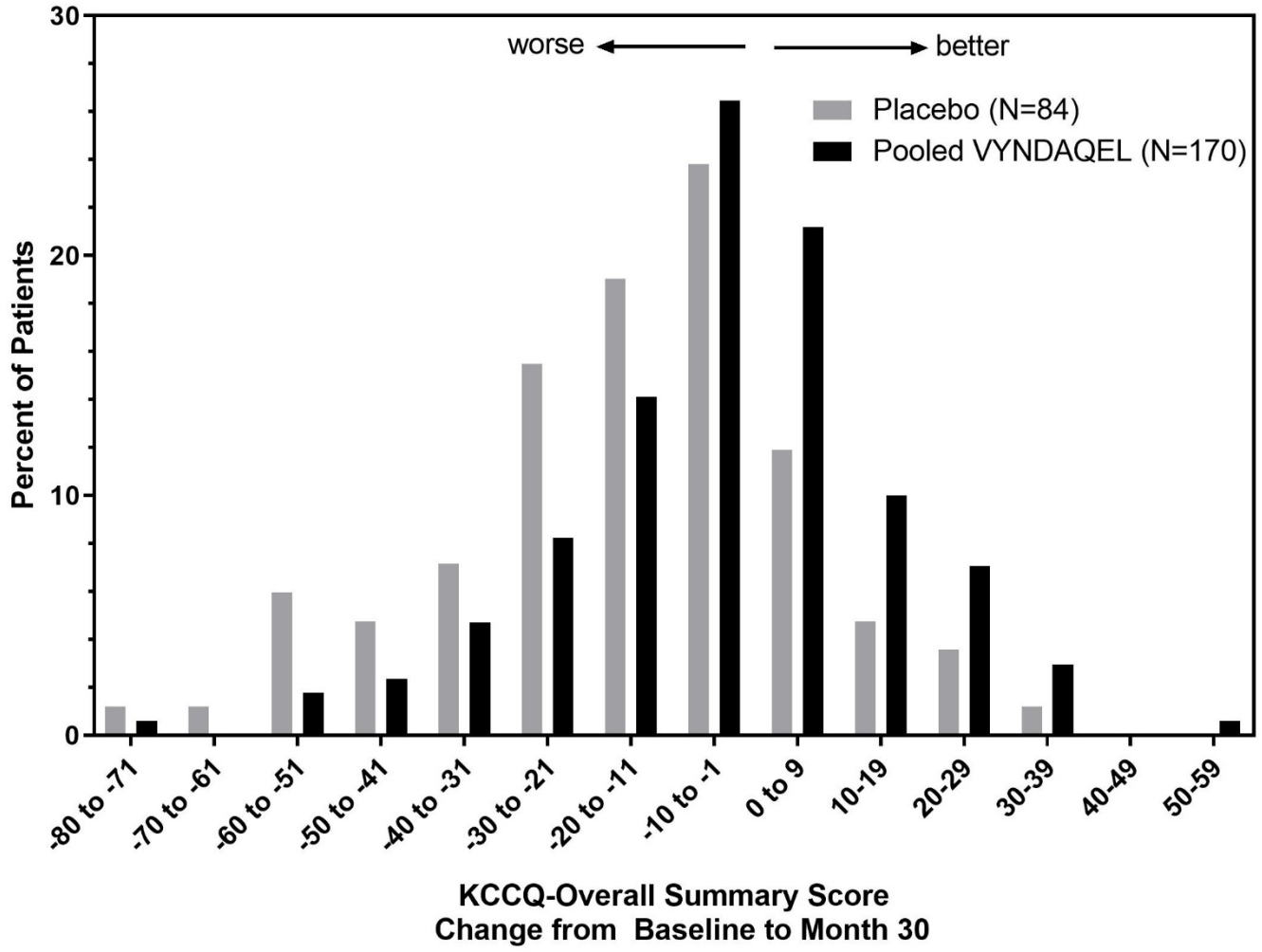


Table 4: 6MWT Distance and KCCQ-OS Scores

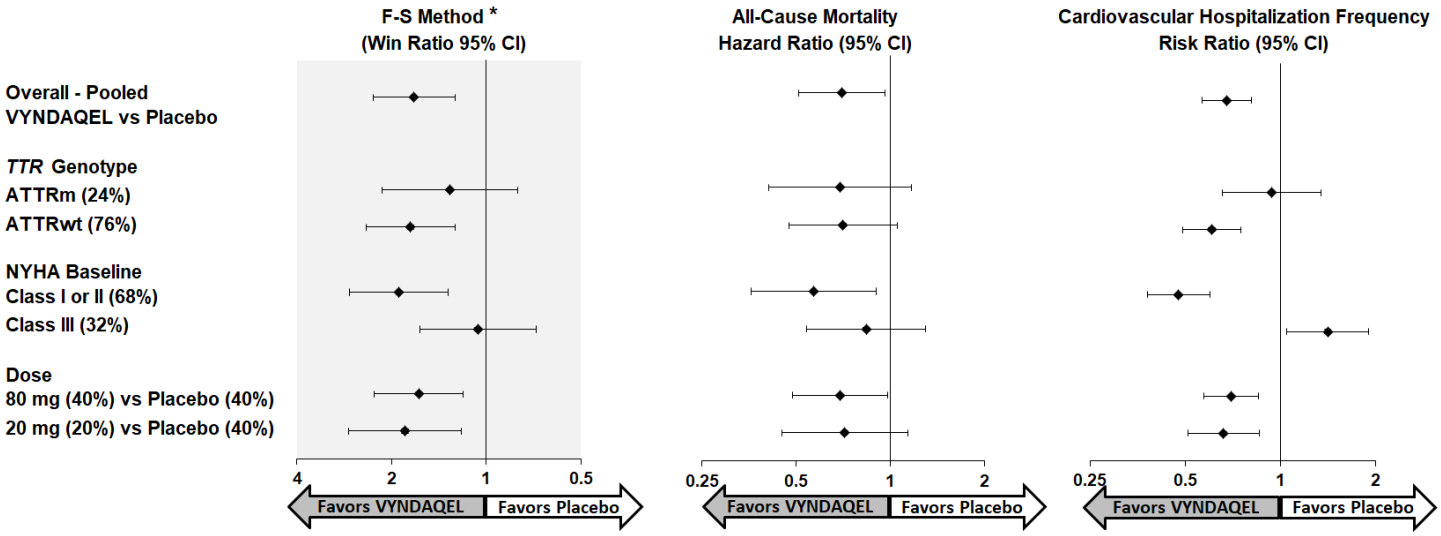
Endpoints	Baseline Mean (SD)		Change from Baseline to Month 30, LS Mean (SE)		Treatment Difference from Placebo LS Mean (95% CI)
	Pooled VYNDAQEL N=264	Placebo N=177	Pooled VYNDAQEL	Placebo	
6MWT (meters)	351 (121)	353 (126)	-55 (5)	-131 (10)	76 (58, 94)
KCCQ-OS	67 (21)	66 (22)	-7 (1)	-21 (2)	14 (9, 18)

Abbreviations: 6MWT = 6-Minute Walk Test; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; SD = standard deviation; LS = least squares; SE = standard error; CI = confidence interval

Results from the F-S method represented by win ratio for the combined endpoint and its components (all-cause mortality and frequency of CV-related hospitalization) consistently favored VYNDAQEL versus placebo across all subgroups (wild type, variant and NYHA Class I & II, and III), except for CV-related hospitalization frequency in NYHA Class III (Figure 4). Win ratio is the number of pairs of VYNDAQEL-treated patient

"wins" divided by number of pairs of placebo patient "wins." Analyses of 6MWT and KCCQ-OS also favored VYNDAQEL relative to placebo within each subgroup.

Figure 4: Results by Subgroup, Dose, and Components of Primary Analysis



Abbreviations: ATTRm = variant transthyretin amyloid, ATTRwt = wild type transthyretin amyloid, F-S = Finkelstein Schoenfeld, CI = Confidence Interval
*F-S results presented using win ratio (based on all-cause mortality and frequency of cardiovascular hospitalization)
Heart transplants and cardiac mechanical assist devices treated as death.

Results of the primary analysis, 6MWT at Month 30 and KCCQ-OS at Month 30 were statistically significant for both the 80-mg and 20-mg doses of VYNDAQEL vs. placebo, with similar results for both doses.

16. HOW SUPPLIED/STORAGE AND HANDLING

VYNDAQEL 20-mg (tafamidis meglumine) soft gelatin capsules are yellow, opaque, oblong, and printed with "VYN 20" in red and supplied in the following package configurations:

VYNDAQEL Capsules		
Package Configurartions	**Strength**	**NDC**
Carton of 4 intermediary cartons. Each intermediary carton contains 3 blister cards. Each blister card contains 10 capsules. (120 total capsules)	20 mg	NDC 0069-1975-40

VYNDAMAX 61-mg (tafamidis) soft gelatin capsules are reddish brown, opaque, oblong, and printed with "VYN 61" in white and supplied in the following package configurations:

VYNDAMAX Capsules		
Package Configuration	**Strength**	**NDC**
Carton of 3 blister cards. Each blister card contains 10 capsules. (30 capsules total)	61 mg	NDC 0069-8730-30

Store VYNDAQEL and VYNDAMAX at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*.

17. PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Pregnancy
Report pregnancies to the Pfizer reporting line at 1-800-438-1985. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation
Advise females not to breastfeed during treatment with VYNDAQEL or VYNDAMAX *[see Use in Specific Populations (8.2)]*.

Transthyretin Amyloidosis Outcome Survey (THAOS)
Advise all patients prescribed VYNDAQEL or VYNDAMAX of the availability of the Transthyretin Amyloidosis Outcome Survey (THAOS) registry, that their participation is voluntary, and may involve long-term follow-up. THAOS is an international disease registry designed to assess disease progression, genotype/phenotype relationships, and the impact of interventions, including VYNDAQEL and VYNDAMAX on disease progression. For information regarding the registry, visit www.thaos.net.

This product's label may have been updated. For full prescribing information, please visit www.pfizer.com.

LAB-0497-0.7

PATIENT INFORMATION

VYNDAQEL® (VIN-duh-kel) (tafamidis meglumine) capsules	VYNDAMAX™ (VIN-dah-max) (tafamidis) capsules

What is VYNDAQEL and VYNDAMAX?

VYNDAQEL and VYNDAMAX are prescription medicines used to treat adults with cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) to reduce death and hospitalization related to heart problems.

It is not known if VYNDAQEL and VYNDAMAX are safe and effective in children.

Before taking VYNDAQEL or VYNDAMAX, tell your healthcare provider about all your medical conditions, including if you:

- have liver problems.
- are pregnant or plan to become pregnant. VYNDAQEL and VYNDAMAX may harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with VYNDAQEL or VYNDAMAX. You may also report your pregnancy by calling the Pfizer reporting line at 1-800-438-1985.
- are breastfeeding or plan to breastfeed. It is not known if VYNDAQEL or VYNDAMAX passes into your breast milk. You should not breastfeed during treatment with VYNDAQEL or VYNDAMAX. Talk to your healthcare provider about the best way to feed your baby during treatment with VYNDAQEL or VYNDAMAX.

Tell your healthcare provider about all the medicines you take including any prescription or over-the-counter medicines, vitamins, and herbal supplements.

How should I take VYNDAQEL or VYNDAMAX?

- Take **either** VYNDAQEL **or** VYNDAMAX exactly as your healthcare provider tells you to.
- Take **either** VYNDAQEL **or** VYNDAMAX capsule(s) 1 time a day.
- VYNDAQEL or VYNDAMAX capsule(s) should be swallowed whole and not crushed or cut.
- If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the next dose at your regularly scheduled time. Do not take 2 doses at the same time.
- There is a Transthyretin Amyloidosis Outcome Survey (THAOS) registry for people who receive treatment with VYNDAQEL or VYNDAMAX. Talk to your healthcare provider about how you can take part in this registry. For more information about this registry, go to www.thaos.net.

What are the possible side effects of VYNDAQEL and VYNDAMAX?

There were no known side effects that happened during treatment with VYNDAQEL or VYNDAMAX in people with cardiomyopathy of transthyretin-mediated amyloidosis.

You may report side effects to FDA at 1-800-FDA-1088.

How should I store VYNDAQEL and VYNDAMAX?

- Store VYNDAQEL and VYNDAMAX capsules at room temperature between 68°F to 77°F (20°C to 25°C).
- **Keep VYNDAQEL and VYNDAMAX and all medicines out of the reach of children.**

General information about the safe and effective use of VYNDAQEL and VYNDAMAX.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use VYNDAQEL or VYNDAMAX for a condition for which it was not prescribed. Do not give VYNDAQEL or VYNDAMAX to other people, even if they have the same symptoms you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about VYNDAQEL or VYNDAMAX that is written for healthcare professionals.

What are the ingredients in VYNDAQEL and VYNDAMAX?

VYNDAQEL:

Active ingredient: tafamidis meglumine

Inactive ingredients: ammonium hydroxide 28%, brilliant blue FCF, carmine, ethyl alcohol, gelatin, glycerin, iron oxide (yellow), isopropyl alcohol, polyethylene glycol 400, polysorbate 80, polyvinyl acetate phthalate, propylene glycol, purified water, sorbitan monooleate, sorbitol, and titanium dioxide

VYNDAMAX:

Active ingredient: tafamidis

Inactive ingredients: ammonium hydroxide 28%, butylated hydroxytoluene, ethyl alcohol, gelatin, glycerin, iron oxide (red), isopropyl alcohol, polyethylene glycol 400, polysorbate 20, povidone (K-value 90), polyvinyl acetate phthalate, propylene glycol, purified water, sorbitol, and titanium dioxide

Distributed by

Pfizer Labs

Division of Pfizer Inc, NY, NY 10017

LAB-0573-0.6

For more information, go to www.vyndaqel.com or call 1-800-438-1985.

This Patient Information has been approved by the U.S. Food and Drug Administration Issued: 05/2019

JAMA | Original Investigation

Financial Eligibility Criteria and Medication Coverage for Independent Charity Patient Assistance Programs

So-Yeon Kang, MPH, MBA; Aditi Sen, PhD; Ge Bai, PhD, CPA; Gerard F. Anderson, PhD

Editorial page 405

Supplemental content

IMPORTANCE Although independent charity patient assistance programs improve patient access to costly prescription drugs, recent federal investigations have raised questions about their potential to increase pharmaceutical spending and to violate the federal Anti-Kickback Statute. Little is known about the design of the programs, patient eligibility, or drug coverage.

OBJECTIVE To examine the eligibility criteria of the independent charity patient assistance programs and the drugs covered by them.

DESIGN, SETTING, AND PARTICIPANTS Descriptive cross-sectional study of the 6 largest independent charities offering patient assistance programs for patients including, but not limited to, Medicare beneficiaries in 2018. These charities offered 274 different disease-specific patient assistance programs. Drugs were identified for subgroup analysis that had any use reported on the Medicare Part D spending dashboard and any off-patent brand-name drugs that incurred more than $10 000 in Medicare spending per beneficiary in 2016.

EXPOSURES Support by independent charity patient assistance programs.

MAIN OUTCOMES AND MEASURES The primary outcomes were the characteristics of patient assistance programs, including assistance type, insurance coverage (vs uninsured), and income eligibility. The secondary outcomes were the cost of the drugs covered by the patient assistance programs and the coverage of expensive off-patent brand-name drugs vs substitutable generic drugs.

RESULTS Among the 6 independent charity foundations included in the analysis, their total revenue in 2017 ranged from $24 million to $532 million, and expenditures on patient assistance programs ranged from $24 million to $353 million, representing on average, 86% of their revenue. Of the 274 patient assistance programs offered by these organizations, 168 (61%) provided only co-payment assistance, and the most common therapeutic area covered was cancer or cancer treatment–related symptoms (113 patient assistance programs; 41%). A total of 267 programs (97%) required insurance coverage as an eligibility criterion (ie, excluded uninsured patients). The most common income eligibility limit was 500% of the federal poverty level. The median annual cost of the drugs per beneficiary covered by the programs was $1157 (interquartile range, $247-$5609) compared with $367 (interquartile range, $100-$1500) for the noncovered drugs. Off-patent brand-name drugs (cost: >$10 000) were covered by a mean of 3.1 (SD, 2.0) patient assistance programs, whereas their generic equivalents were covered by a mean of 1.2 (SD, 1.0) patient assistance programs.

CONCLUSIONS AND RELEVANCE In 2018, among 274 patient assistance programs operated by the 6 independent charity foundations, the majority did not provide coverage for uninsured patients. Medications that were covered by the patient assistance programs were generally more expensive than those that were not covered.

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Patient assistance programs help patients afford prescription drugs by subsidizing their out-of-pocket costs. Federal health programs, including Medicare, prohibit the use of manufacturer-sponsored drug-specific patient assistance programs due to the federal Anti-Kickback Statute that forbids manufacturers from offering any remuneration for a federally reimbursable item.[1] However, federal health programs allow patients to participate in disease-specific independent charity patient assistance programs based on the assumption that these programs do not violate anti-kickback laws.[2] Pharmaceutical companies may make tax-deductible donations to these disease-specific funds.

Independent charity patient assistance programs have grown rapidly since the enactment of the Medicare Modernization Act of 2003, which became effective in 2006. Between 2007 and 2016, the total amount of patient assistance granted by the 5 largest independent charities increased by 588%.[3,4] Independent charity patient assistance programs must observe legal constraints on their program design and distribution of funds, and remain independent regardless of the source of their revenue.[5]

However, 7 pharmaceutical companies paid multimillion-dollar settlements between 2017 and 2019 to the Department of Justice for allegedly requiring some independent charities to design patient assistance programs that restricted benefits to only those companies' drugs.[6-9] These settlements have further prompted anti-kickback concerns within the context of patient assistance programs. Researchers have discussed the profit motives behind the charitable donations made to patient assistance programs,[3,10] examined patient assistance programs in limited settings,[11-13] and studied manufacturer-sponsored programs.[14] However, little is known about independent charity patient assistance programs and the financial support they provide.

This study examined independent charity patient assistance programs operated by 6 foundations that have the largest revenue contribution to the programs and disclosed program details. This study also assessed the characteristics of the patient assistance programs and their medication coverage; specifically, how covered vs uncovered drugs varied in terms of the price and coverage of brand-name drugs vs their generic equivalents.

Key Points

Question What are the characteristics of independent charity patient assistance programs?

Findings In this cross-sectional study of 6 independent charity organizations that included 274 patient assistance programs in 2018, 97% of the programs excluded uninsured patients, and the most common income eligibility limit was 500% of the federal income poverty level. In the drug-level analysis, the median 2016 Medicare Part D spending per beneficiary was $1157 for medications covered by these programs compared with $367 for the medications not covered.

Meaning The majority of independent charity patient assistance programs in this study did not cover uninsured patients and were more likely to cover more expensive medications.

Methods

The institutional review board at Johns Hopkins University, Bloomberg School of Public Health, provided an exemption for this study.

Sample Identification

Because there is no central database of patient assistance programs or an existing systematic study, the GuideStar nonprofit organization database was searched for 501(c)(3) charities that had annual revenues of at least $10 million in 2017 and National Taxonomy of Exempt Entities codes in category E (health care) or G (voluntary health associations and medical disciplines). To identify independent charity foundations offering patient assistance programs, the following keywords were used: *patient assistance, financial assistance, prescription (drug) assistance, co(-)pay(ment),* and *charitable assistance*. This query returned 222 nonprofit organizations. Foundations and organizations were excluded if access was restricted to local members in specific regions along with entities that did not provide monetary support for prescription medications, such as manufacturer-sponsored foundations, advocacy organizations, hospitals, and community health systems. The Caring Voice Coalition also was excluded because it discontinued its patient assistance programs due to recent federal anti-kickback allegations. This selection strategy identified 8 nonprofit, independent charity organizations that offer monetary assistance to patients to cover their prescription drug costs.

The following 4 criteria were used to identify independent charity organizations or foundations that operate patient assistance programs and were suitable for the empirical analysis: (1) allocate more than 50% of its revenue for patient assistance programs; (2) disclose the patient eligibility criteria for patient assistance programs; (3) disclose the names of covered medications and associated funding amounts for disease-specific patient assistance programs; and (4) appear on the Medicare patient assistance program website. From their websites, we reviewed each organization's latest annual reports and collected details of the patient assistance programs offered by the charities.[15,16]

We identified Medicare Part D drugs covered by 2 specific foundations that were listed on the Medicare website and had reported drug use data on the Medicare Part D spending dashboard for 2016.[17] For each drug, we obtained the Medicare Part D spending per beneficiary in 2016 from the Medicare Part D spending dashboard and calculated the mean out-of-pocket cost per beneficiary using Medicare Prescription Drug Event data. To obtain the out-of-pocket cost per beneficiary, we used the total amount paid by the beneficiary, which excludes the amount paid by the Medicare Part D low-income subsidy and other third-party payers such as group health plans and governmental programs (eg, the US Department of Veterans Affairs).[18]

To identify specialty drugs, we used the threshold for the Medicare Part D specialty tier defined by the Centers for Medicare & Medicaid Services as monthly spending greater than

$600 per beneficiary in 2016.[19] From the list of specialty drugs, we then identified off-patent drugs that incurred costs of greater than $10 000 per beneficiary in Medicare spending in 2016 that had generic equivalents available on the market as of December 2018.[20]

Outcomes

We examined the assistance type (eg, co-payment reimbursement or subsidy of health insurance premium), disease areas, health insurance requirements, income eligibility, number of drugs covered by a patient assistance program, and maximum annual amount provided by an independent charity patient assistance program.

The median 2016 spending for Medicare Part D drugs covered by patient assistance programs was compared with Medicare Part D drugs not covered by the programs. For the drugs that were covered by patient assistance programs, we also studied the coverage of patients' out-of-pocket costs and compared it with total Medicare spending per drug per beneficiary. The Medicare Part D drugs were grouped based on 2016 spending per beneficiary and we examined the proportion of total drugs in each group covered by independent charity patient assistance programs.

In addition, we analyzed Medicare Part D off-patent brand-name drugs covered by independent charity patient assistance programs with costs of greater than $10 000 per beneficiary in 2016. We also examined the number of patient assistance programs covering brand-name drugs and their generic equivalents.

Data Analysis

Descriptive statistics were used to characterize independent charities offering patient assistance programs, and the features and drugs covered by these programs. Means were used to report normally distributed data, medians for data that are not normally distributed, and proportions as appropriate. Excel version 15.24 (Microsoft) was used for all the analyses.

Results

Among the 8 independent charity organizations that offer monetary assistance to patients and had annual revenues of at least $10 million in 2017, only 2 organizations (the Patient Access Network [PAN] Foundation and the HealthWell Foundation) met all 4 criteria used to determine suitability for the empirical analysis. These 2 foundations were the only ones listed on the Medicare website, which also identifies drugs covered by the patient assistance programs.[21] The other 6 foundations or organizations did not meet at least 1 criterion used to determine suitability for the empirical analysis. The National Organization of Rare Disorders and the Assistance Fund did not disclose sufficient data for the analysis, and the other 4 organizations did not disclose the names of the covered drugs or the funding amount.

The PAN Foundation and the HealthWell Foundation met all 4 criteria and made up the empirical analysis sample. In aggregate, the 2 foundations accounted for 50% of the total spending represented by the 8 independent charity organizations in the broader sample that appears in **Table 1**. Four organizations (CancerCare Co-Payment Assistance Foundation, Good Days, Patient Advocate Foundation Co-Pay Relief, and Patient Services Incorporated) disclosed the patient eligibility criteria for the patient assistance programs, but did not disclose the specific drugs and amount of funding they provide. Six organizations (CancerCare Co-Payment Assistance Foundation, Good Days, the HealthWell Foundation, the PAN Foundation, the Patient Advocate Foundation Co-Pay Relief, and Patient Services Incorporated) were included in the analysis on characteristics of the patient assistance programs (**Table 2**).

Characteristics of Independent Charities Offering Patient Assistance Programs

The characteristics of the 8 independent charity foundations that offered patient assistance programs and reported annual revenue of more than $10 million in 2017 appear in Table 1. Six of the 8 organizations were established during or after 2003. Among the 6 independent charity foundations included in the analysis, their total revenue in 2017 ranged from $24 million to $532 million, and expenditures on patient assistance programs ranged from $24 million to $353 million, representing on average, 86% of their revenue. The disclosure practices of these organizations varied. Only the PAN Foundation and the HealthWell Foundation disclosed the names of drugs, the dollar amount of maximum annual assistance they cover, and the patient eligibility criteria. The CancerCare Co-Payment Assistance Foundation was the only organization that disclosed its corporate donors (6 of its 7 donors that contributed >$1 million in 2017 were pharmaceutical companies).

Features of Patient Assistance Programs

The characteristics of the 274 independent charity patient assistance programs that disclosed patient eligibility criteria and were operated by the 6 independent charity foundations appear in Table 2. The patient assistance programs covered medications for a wide variety of diseases as of December 2018. The financial support offered by the patient assistance programs took several forms. There were 168 patient assistance programs (61%) that provided only co-payment assistance, 9 programs (3%) offered only assistance to subsidize the cost of health insurance premiums, and 90 programs (33%) allowed patients to choose between co-pay and insurance premium assistance. None of the patient assistance programs offered free drugs. The most common therapeutic areas covered were cancer or cancer treatment-related symptoms (113 programs; 41%) and genetic or rare diseases (93 programs; 34%).

Eligibility for all of the patient assistance programs was based on the following criteria: annual household income measured by the federal poverty level (FPL) guidelines, insurance status, physician endorsement, prescription information, and proof of receiving treatment in the United States. Of the patient assistance programs, 267 (97%) required insurance coverage as an eligibility criterion and 259 (94%) used 400% or 500% of the FPL as their income eligibility limit.

The independent charity foundations varied the FPL income eligibility limits across different patient assistance programs. For example, the HealthWell Foundation used 400%

Table 1. Characteristics of Major Independent Charity Foundations Offering Patient Assistance Programs

Profile of Independent Charity Foundation					Type of Information Disclosure			
Name	Year Established	Total Revenue in Millions, $[a]	Patient Assistance Expense in Millions, $[a]	Expense Ratio, %[a,b]	Disclosure Description of Donors[a]	Patient Eligibility Available?	Names of Drugs and Funding Amount Covered Available?	Listed on Medicare Patient Assistance Program Website?
Included in Empirical Analysis								
HealthWell Foundation	2003	359	353	98	Partial disclosure[c]	Yes	Yes	Yes
Patient Access Network Foundation	2004	532	348	65	Not available	Yes	Yes	Yes
Excluded From Empirical Analysis								
Good Days	2005	180	250	139	Not available	Yes	No	No
Patient Advocate Foundation Co-Pay Relief	2004	225	183	81	Names only	Yes	No	No
Patient Services Incorporated	1989	119	93	78	Names only	Yes	No	No
CancerCare Co-Payment Assistance Foundation	2008	24	24	100	Names by the level of funding	Yes	No	No
National Organization for Rare Disorders	1983	48	25	52	Not available	No	No	No
The Assistance Fund	2009	164	120	73	Not available	No	No	No

[a] Data are from 2017 annual reports and each organization's form 990.

[b] Calculated as patient assistance expense divided by total revenue.

[c] Disclosed the names of only noncorporate sponsors.

of the FPL as the income eligibility limit for patient assistance programs offering $25 000 as the maximum annual assistance, but used 500% of the FPL for patient assistance programs offering $2500 as the maximum annual assistance. Similarly, the PAN Foundation used 400% of the FPL as the income eligibility limit for patient assistance programs offering $12 000 as the maximum annual assistance, but used 500% of the FPL for patient assistance programs offering $800 as the maximum annual assistance.

Drugs Covered by Patient Assistance Programs

We also examined the characteristics of the 123 patient assistance programs offered by the 2 foundations (PAN and HealthWell) with data that permitted drug-level analysis. These foundations were the only ones listed on the Medicare patient assistance program website (Table 1). Of the 123 patient assistance programs offered by the 2 foundations, 100% required patients to have insurance and 99.2% used 400% or 500% of the FPL as their income eligibility limit (eTable in the Supplement). The characteristics of the 123 patient assistance programs offered by these 2 foundations (eTable in the Supplement) were similar to those reported in Table 2. The characteristics of the patient assistance programs offered by the PAN and the HealthWell foundations were included in both the eTable in the Supplement and in Table 2.

Among the 2828 Medicare Part D drugs listed on the Medicare spending dashboard, 1156 (41%) were covered by at least 1 of the 123 independent charity patient assistance programs offered by the PAN and HealthWell foundations and the remaining 1672 (59%) were not covered. The median 2016 Medicare Part D spending per beneficiary on drugs covered by 123 patient assistance programs was $1157 (interquartile range [IQR], $247-$5609), which was 315% of the median spending for drugs that were not covered ($367; IQR, $100-$1500). The maximum level of annual assistance available was sufficient to cover the mean Medicare beneficiary's out-of-pocket cost for 1152 of the 1156 drugs (99.7%). There was no information available to determine how often the maximum level was provided.

The median number of drugs covered by a disease-specific patient assistance program was 20 (IQR, 6-32). Drugs produced by a single manufacturer had a higher median number that were covered by patient assistance programs (13 [IQR, 5-25] drugs) compared with drugs produced by multiple manufacturers (6 [IQR, 3-11] drugs). The maximum annual assistance amount varied by patient assistance program and ranged from a low of $500 (for drugs to treat postmenopausal osteoporosis from the PAN Foundation) to a high of $30 000 (for drugs to treat hepatitis C from the HealthWell Foundation), with a mean patient assistance amount of $7283 (SD, $4801).

There was a monotonic relationship between the annual cost of the drug and the likelihood that the drug was included in a patient assistance program (**Table 3**). Based on 2016 Medicare Part D spending per beneficiary, drugs were covered by at least 1 patient assistance program for 36% of nonspecialty drugs costing less than $7200, 52% of drugs costing between $7200 and $10 000, 73% of specialty drugs costing between $10 000 and $30 000, and 83% of specialty drugs costing more than $30 000.

Table 2. Characteristics of Patient Assistance Programs Offered by 6 Independent Charity Foundations[a]

Characteristics	Patient Assistance Programs (N = 274)
Assistance type, No. (%)	
Co-pay only	168 (61)
Co-pay or insurance premium (patient's choice)	90 (33)
Insurance premium only	9 (3)
Unknown	7 (3)
Therapeutic areas, No. (%)	
Cancer or cancer treatment-related symptom	113 (41)
Genetic or rare disease[22]	93 (34)
Autoimmune disease	13 (5)
Cardiovascular, central nervous system, or infectious disease	22 (8)
Other[b]	33 (12)
Health insurance requirement, No. (%)	267 (97)
Income eligibility limit defined by the FPL, No. (%)[23]	
300%[c]	8 (3)
400%[d]	119 (43)
500%[e]	140 (51)
600%[f]	7 (3)
Annual maximum assistance amount	
No. of programs[g]	163
Mean (SD), $	5825 (4069)

Abbreviation: FPL, federal poverty level.

[a] Includes patient assistance programs run by the CancerCare Co-Payment Assistance Foundation, Good Days, the HealthWell Foundation, the Patient Access Network Foundation, the Patient Advocate Foundation Co-Pay Relief, and Patient Services Incorporated. Data are from a 2018 survey of independent charity patient assistance programs conducted by the authors.

[b] Includes diabetic foot ulcers, atopic dermatitis, macular diseases, anemia associated with chronic renal failure, venous leg ulcers, chronic pain, osteoporosis, ulcerative colitis, retinal diseases, electrolyte imbalance, movement disorders, iron overload, pulmonary fibrosis, immunosuppressive treatment for organ transplant recipients, etc.

[c] Defined as $36 420 for an individual and $75 300 for a family of 4.

[d] Defined as $48 560 for an individual and $100 400 for a family of 4.

[e] Defined as $60 700 for an individual and $125 500 for a family of 4.

[f] Defined as $72 840 for an individual and $150 600 for a family of 4.

[g] Only 163 programs disclosed the maximum assistance amount.

Table 3. Distribution of Medicare Part D Spending per Beneficiary for Drugs Covered by 1 or More Independent Charity Patient Assistance Programs in 2018

	Covered by ≥1 Patient Assistance Programs, No./Total No. (%)[a]		
	Drugs Produced by a Single Manufacturer[b]	Drugs Produced by Multiple Manufacturers[c]	Total
Average annual Medicare Part D spending per drug per beneficiary in 2016, $			
<7200	566/1654 (34)	324/808 (40)	890/2462 (36)
7200-10 000	31/58 (53)	1/3 (33)	32/61 (52)
10 000-30 000	93/125 (74)	3/6 (50)	96/131 (73)
>30 000	136/164 (83)	2/2 (100)	138/166 (83)

[a] Data are from the Medicare Part D spending dashboard.

[b] The majority were brand-name drugs, but some generic drugs were produced by a single manufacturer.

[c] The majority were generic drugs, but some brand-name drugs were produced by multiple manufacturers.

Patient Assistance Program Coverage of Brand-Name Drugs With Available Generic Equivalents

There were 38 Medicare Part D off-patent brand-name drugs with a generic equivalent available in 2018 that were covered by at least 1 of the 123 independent charity patient assistance programs (costing >$10 000 per beneficiary in 2016 Medicare spending). Among the 38 drugs, 6 did not have a patient assistance program covering the generic equivalents, 12 had fewer patient assistance programs covering the generic equivalents than the brand-name versions, and 20 had the same number of patient assistance programs covering the brand-name and generic versions.

Among 18 drugs, the brand-name versions (cost: >$10 000) were covered by a mean of 3.1 (SD, 2.0) patient assistance programs and their generic equivalents were covered by a mean of 1.2 (SD, 1.0) patient assistance programs. For example, there were 8 patient assistance programs covering Velcade, but only 1 patient assistance program covering

its generic equivalent (bortezomib) (**Table 4**). Similarly, there were 4 patient assistance programs that covered Targretin (costs Medicare >$100 000/year per beneficiary), but only 2 patient assistance programs covered the generic equivalents (bexarotene; there are 4 generic equivalents on the market). Among the 18 drugs, 12 (67%) were in protected classes, which must be covered by all Medicare Part D plans (8 antineoplastics, 2 antiretrovirals, and 2 antipsychotics).

Discussion

This study found that 97% of the patient assistance programs offered by 6 independent charity foundations did not provide financial assistance to uninsured patients based on disclosed patient eligibility criteria. The programs were more likely to cover expensive specialty drugs and brand-name drugs than less-expensive brand-name drugs and generic equivalents. The other independent charity foundations did not disclose details of their patient assistance programs or donors.

For patients taking expensive drugs, some patient assistance programs may play an important part in defraying the cost of needed medications. These patients may have difficulty affording their medications when they do not have health insurance coverage for the drugs, when they are in the deductible phase of the benefit, or when they reach the coverage gap (the period in which they are required to pay a larger share of total drug costs). This is especially a problem for Medicare enrollees who are prescribed high-cost specialty drugs because most Medicare Part D plans charge higher coinsurance for these specialty drugs and there is no catastrophic cap in the Medicare program. Thus, out-of-pocket costs can reach thousands of dollars.[24] For this reason, independent charity foundations offering patient assistance programs to these patients are entitled to receive tax-deductible donations from pharmaceutical companies. However, the findings from this study suggest that several features of the programs may limit their usefulness to financially needy patients and bolster the use of expensive drugs.

The exclusion of uninsured patients from the eligibility criteria was a uniform pattern across patient assistance programs. Although the patient assistance programs covered Medicare patients, they also covered non-Medicare patients. The programs often featured the number of insured patients as an important performance metric.[25,26] Because covering an insured patient requires less money compared with covering an uninsured patient who needs the same drug, one possible explanation for excluding uninsured patients is that the programs attempted to use their limited funding to assist as many beneficiaries as possible. The study also found that 46% of the patient assistance programs provided insurance premium assistance, which by design is not applicable to uninsured patients. Taken together, enhancing patient assistance programs to include uninsured patients, who are likely to face greater affordability challenges than insured patients, may be an area for improvement.

The finding regarding preferential coverage of high-priced specialty and brand-name drugs over generic equivalents adds to a growing body of literature suggesting that co-payment assistance programs may motivate physicians and patients to choose treatment options with a lower out-of-pocket cost burden despite the higher total cost and the availability of lower-cost alternatives. Prior studies found that the co-payment coupons steered privately insured patients toward brand-name drugs and away from generic equivalents.[27-30] The current study extends this literature to patient assistance programs offered by independent charity foundations.

Greater use of high-cost specialty drugs has been found to be associated with an increase in out-of-pocket drug cost among Medicare Part D enrollees who do not receive the low-income subsidy.[24] By reimbursing patients for their entire out-of-pocket spending, patient assistance programs can desensitize beneficiaries to the total price of the drug and thus undermine the purpose of co-payments and coinsurance. This is of particular concern for the Medicare Part D program because patients taking more expensive drugs will progress more quickly to the catastrophic coverage phase when Medicare pays 80% of the cost of the drug.[31] On that account, federal guidelines require independent charities to provide financial assistance for all medications approved by the US Food and Drug Administration including generic drugs and prohibit independent charity foundations from designing patient assistance programs that favor the use of expensive brand-name drugs. However, this study and recent anti-kickback allegations suggest the need for better monitoring and a compliance framework to ensure financial support for lower-cost alternatives in the programs.

Another finding of this study was the wide variation in disclosure practices across the patient assistance programs. This lack of transparency was an impediment for researchers accessing program details and donor information and assessing the role of patient assistance programs.[14] The financial contributions from pharmaceutical companies are neither disclosed for most independent charity patient assistance programs, nor is the actual allocation of financial assistance across specific drugs.[32] Given the increasing scale and scope of independent charity patient assistance programs, more transparency is needed to facilitate monitoring to ensure the activities of these programs are aligned with their charitable missions.

Limitations

This study has several limitations. First, no data were available regarding the size and profile of beneficiaries assisted by the independent charity patient assistance programs, the actual assistance dollar amounts disbursed to beneficiaries for specific drugs, or the amount of drug use that was induced by these programs. Therefore, the correlation between the actual use of the patient assistance programs with drug spending and drug use metrics cannot be assessed.

Second, how patient assistance programs make drug coverage decisions when they receive patient applications cannot be determined due to the lack of publicly available data. From this data set, we cannot determine whether a patient or drug is actually covered or not.

Table 4. Characteristics of Off-Patent Brand-Name Drugs Covered by Medicare Part D That Had Fewer Independent Charity Patient Assistance Programs Covering the Corresponding Generic Drugs[a]

Off-Patent Brand-Name Drug	Active Ingredients	Annual Mean Medicare Spending per Beneficiary, $	No. of Patient Assistance Programs Included in Empirical Analysis					
			Brand-Name Drugs			Generic Drugs		
			Total	PAN Foundation	HealthWell Foundation	Total	PAN Foundation	HealthWell Foundation
Sabril	Vigabatrin	172 251	1	1	0	0	0	0
Targretin	Bexarotene	108 112	4	2	2	2	2	0
Tasmar	Tolcapone	64 931	2	1	1	1	1	0
Zytiga	Abiraterone acetate	50 656	1	1	0	0	0	0
Treanda	Bendamustine hydrochloride	36 468	7	4	3	1	1	0
Velcade	Bortezomib	28 059	8	5	3	1	1	0
Vidaza	Azacitidine	24 057	4	1	3	3	1	2
Zyflo CR	Zileuton	20 990	3	0	3	1	1	0
Torisel	Temsirolimus	17 636	4	0	4	2	0	2
Ampyra	Dalfampridine	16 372	2	1	1	1	1	0
Sandostatin	Octreotide acetate	15 885	3	1	2	2	1	1
Zyflo	Zileuton	14 938	4	1	3	1	1	0
Miacalcin	Calcitonin-salmon	12 875	3	2	1	2	1	1
Abilify	Aripiprazole	11 765	1	1	0	0	0	0
Rilutek	Riluzole	11 548	3	0	3	1	1	0
Reyataz	Atazanavir	11 456	1	1	0	0	0	0
Lexiva	Fosamprenavir	11 111	1	1	0	0	0	0
Fusilev	Levoleucovorin	10 215	4	1	3	3	1	2
Total			56	24	32	21	13	8

Abbreviation: PAN, Patient Access Network.

[a] Data are from a 2018 survey of independent charity patient assistance programs conducted by the authors.

Third, the empirical analysis of drug use was limited to 2 foundations. It is possible that other charities that operate patient assistance programs have practices that are different from the 2 foundations examined.

Fourth, this study assumed that generic substitution was always possible (ie, both a brand-name and a generic version of a particular drug were available) and did not take into account physician and patient preference.

Conclusions

In 2018, among 274 patient assistance programs operated by the 6 independent charity foundations, the majority did not provide coverage for uninsured patients. Medications that were covered by the patient assistance programs were generally more expensive than those that were not covered.

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Letters

RESEARCH LETTER

Initial Experience Prescribing Commercial Tafamidis, the Most Expensive Cardiac Medication in History

Tafamidis is a stabilizer of the transthyretin (TTR) protein tetramer, which was recently shown to reduce all-cause mortality and cardiovascular hospitalizations.[1] Tafamidis was approved by the US Food and Drug Administration on May 3, 2019, for the treating TTR amyloid cardiomyopathy[2] and has a list price of $225 000 per annum.[3] A recent study showed that tafamidis exceeds conventional cost-effectiveness thresholds.[4] In this article, we describe our early experience in prescribing commercial tafamidis. All patients with an established diagnosis of TTR amyloid cardiomyopathy who presented to the Oregon Health & Science University Multidisciplinary Amyloidosis Program and received a prescription for commercial tafamidis were included in the analysis. We did not intentionally exclude women, but all of our consecutive cohort were men. Approval and a waiver of consent because of minimal risk for participants were obtained from the institutional review board of Oregon Health & Science University.

From May through November 2019, 50 consecutive patients (mean [SD] age, 76 [8] years) were prescribed tafamidis and 43 patients (86%) successfully obtained the drug. Only 1 patient (2%) did not have prescription insurance, while 38 patients (76%) had Medicare Part D, 6 (12%) had private insurance, 2 (4%) had Veterans Affairs insurance, and 3 (6%) had other types. Of the 7 (14%) who did not obtain tafamidis, 3 could not afford the out-of-pocket cost, 2 declined further attempts at drug procurement, 1 died before receiving tafamidis, and 1 elected to enroll in a research study. The mean (SD) cost of a 30-day supply of tafamidis was $23 485 ($2). All prescriptions required prior authorization (3 patients [6%] required a prior authorization appeal). Prior to financial assistance, the median and mean (SD) 30-day out-of-pocket costs of tafamidis were $1909 (range, $250-$3144) and $3082 ($5216), respectively (insurers covered a mean [SD] 89% [17%] of the total tafamidis cost). Fifteen patients (30%) qualified for copayment assistance from a foundation and an additional 13 (26%) received financial assistance from the manufacturer (**Table**). All patients who qualified for financial assistance paid $0, while the median and mean (SD) 30-day out-of-pocket costs of tafamidis for patients without financial assistance were $250 (range, $39-$1763) and $1683 ($858), respectively (**Figure**). The median time from prescribing to mailing tafamidis was 26 (range, 12-78) days.

Our initial experience prescribing tafamidis demonstrates that the current system depends heavily on copayment assistance programs. Regulations instituted in 2005 by the US Office of the Inspector General and the US Department of Health and Human Services aimed to ensure compliance of the patient assistance programs with the Anti-Kickback Statute.[5] The most pertinent regulation to patients is that the assistance should be based on reasonable and consistent measures of financial need, requiring certain thresholds to be put in place under which patients may qualify for assistance. There are many elderly individuals who do not qualify for assistance based on these thresholds but have other preexisting competing financial commitments that prohibit them being able to afford the costly copayments. In addition to these eligibility stipulations, the funds in these nonprofit foundations are liable to run out. We have experienced periods during which programs have closed temporarily, causing tremendous uncertainty for patients. In our experience, some of the patients who were initially denied manufacturer assistance had success with an additional level of appeal. In these cases, patients directly appealed to the manufacturer with more granular explanations of unaccounted financial obligations and hardship that may not be captured on an income tax report. Finally, we have an integrated multidisciplinary amyloidosis pro-

Table. Characteristics of Patient Assistance Programs Active During the Study Period

Eligibility criteria	Pfizer Vyndalink[a]	PAN Foundation	HealthWell Foundation	TAF
Disease covered under program	Yes	Yes	Yes	Yes
Medication has to be covered by insurance	Case by case[b]	Yes	Yes	Yes
Medicare only	NA	Yes	No	No
Income falls at or below federal poverty level, %[c]	500	500	400-500	Varies (665 as of December 2019)
US citizen or permanent resident	Yes	No	NA	Yes
Must receive treatment in the US	Yes	Yes	Yes	Yes
Assistance amount (per year), $	Free medication	7800	8000	Varies
Approved period	Up to 1 y	Up to 1 y	Up to 1 y	Up to 1 y
Renewal	Yes	Varies depends on funding	Varies depends on funding	Varies depends on funding

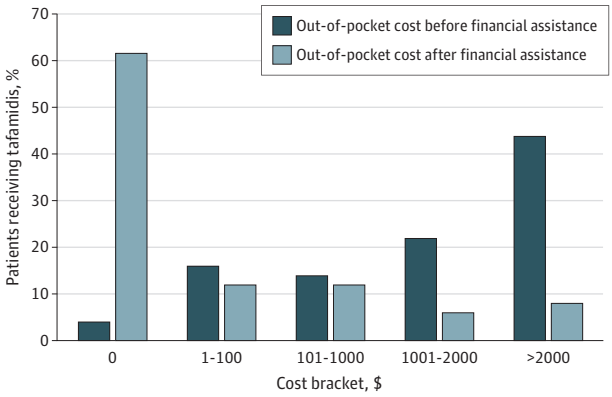
Abbreviations: NA, not applicable; PAN, Patient Access Foundation; TAF, The Assistance Fund.

[a] Pfizer has 2 options: an assistance program or a copay card.

[b] Based on patients' experience, an appeal resulting in successful assistance from Pfizer is possible.

[c] Federal poverty level for 2019 is $12 490 for 1 person and $16 910 for 2 people.

Figure. Tafamidis Out-of-Pocket Costs



Distribution of tafamidis out-of-pocket costs for all patients before any assistance programs were applied to and after 28 patients (56%) received financial assistance.

gram, a specialty pharmacy, and a dedicated pharmacist who spent an average of 1 hour per patient to ensure they can afford tafamidis. As such, our experience might not be easily applicable to other health care settings.

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Disclaimer: The information, conclusions, and opinions expressed are those of the authors, and no endorsement by Federal Office of Rural Health Policy, Health Resources and Services Administration, and the US Department of Health and Human Services is intended or should be inferred.

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COMMENT & RESPONSE

Initial Monthly Cost of Tafamidis—the Real Price for Patients

To the Editor We concur entirely with the Viewpoint by Gurwitz and Maurer[1] on the high price of tafamidis for the treatment of transthyretin amyloidosis cardiomyopathy (ATTR-CM). The authors briefly addressed the potential problem of access and affordability for patients but do not provide details on cost. As this is a disease of the elderly, most patients in the US receiving tafamidis are Medicare beneficiaries. Medicare has a multilayered structure for drug coverage, and patients may be subject to high copayments, which vary depending on several factors, including supplemental insurance. For those with a high copayment, pharmaceutical company–sponsored, income-based financial assistance may be available, and charitable foundations inconsistently have available funds, but both are on a year-to-year basis.

In the 6 months following US Food and Drug Administration approval, we prescribed tafamidis to 80 patients with ATTR-CM through a prescription processed by our integrated health-system specialty pharmacy. Three patients were denied tafamidis by their insurance company, and the initial first-month cost or copayment for the remaining 77 was less than $100 (ranging from $0 to $82) for 26 patients (34%), whereas the remaining 51 patients (66%) had a copayment greater than $1000 (ranging from $1010 to $14 681) with a mean (SD) cost of $2270.45 ($1869). Nineteen patients (25%) were deemed ineligible for financial assistance from Pfizer or other foundations, 12 (16%) were approved for assistance from Pfizer with 4 applications still pending, and 13 (17%) received support from foundations. After copayment assistance, 23 patients (30%) still had a copayment greater than $1000, 9 of whom (12%) decided not to start the medication.

Tafamidis is a life-prolonging medication for patients with ATTR-CM.[2] However, despite assistance, nearly one-third of our patients are faced with a significant financial burden, and the remainder are only guaranteed assistance for 12 months. A beacon of hope for the treatment of ATTR-CM amyloidosis has become an exemplar of the financial burden of certain life-prolonging medications whose price is opaquely set. Now that specific cardiac imaging is available for patients with ATTR-CM,[3] it is recognized as being far more common than initially thought when tafamidis was given orphan drug designation in 2011,[4] and our data underscore the financial burden to a significant proportion of patients. We fully support the conclusion of Gurwitz and Maurer[1] that the opaque mechanism by which the price was set should now be made transparent and subject to review.

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2. Maurer MS, Schwartz JH, Gundapaneni B, et al; ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379(11):1007-1016. doi:10.1056/NEJMoa1805689

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In Reply In commenting on our Viewpoint,[1] Cuddy et al describe the real price of tafamidis for patients with transthyretin amyloid cardiomyopathy (ATTR-CM) cared for at their institution. The findings underscore that insurance coverage for prescription medications and patient assistance programs run by pharmaceutical companies do not shield patients from high drug prices. David Mitchell, founder of Patients for Affordable Drugs, has stated, "drugs don't work if people can't afford them"[2]; "innovation and new drugs should not come at prices that bankrupt people…when they are struggling to maintain their health."[3]

A cost-effectiveness analysis published in 2020[4] indicated that a greater than 90% price reduction (from $225 000 to $16 563 per year) would be necessary to make tafamidis cost-effective at $100 000 per quality-adjusted life-year. Lending greater transparency to the relationship between affordability and access may be the only way to influence pharmaceutical companies to commit to responsible pricing of novel therapies like tafamidis guided by rigorous cost-effectiveness analyses.[5]

We congratulate the authors for sharing this important information, which closely mirrors the experience at one of our centers. We urge other institutions providing care to patients with ATTR-CM to publicize information about the high out-of-pocket costs for tafamidis borne by many patients, which is directly related to its excessively high list price.

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Additional Information: The Meyers Primary Care Institute is a joint endeavor of the University of Massachusetts Medical School, Fallon Health, and Reliant Medical Group.

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CORRECTION

Error in Text: In the Original Investigation titled "Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19)," published online March 27, 2020, errors appeared in the Abstract and Results section. The number of patients with elevated troponin T levels using mechnical ventilation is 31, rather than 41. In addition, the mortality rate of patients without use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers is 21.4% (36 of 168) (P = .13). The article has been corrected online.

1. Guo T, Fan Y, Chen M, et al. Cardiovascular Implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. Published online March 27, 2020. doi:10.1001/jamacardio.2020.1017

Citi Research

Equities

16 May 2017 01:55:17 ET | 17 pages

Pharmaceuticals
Western Europe

The Straw That Could Break the Camel's Back.

DOJ/ OIG Action on Foundation Funding Could Severely Impede Industry Returns

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- **Citi's Take.** The ongoing multiple DoJ/OIG investigations into financial donations by pharmaceutical companies to independent foundations has the potential to severely limit future revenues for several high priced blockbuster Medicare Part D drugs through (i) lowered overall funding for patient out-of-pocket assistance (ii) lesser ability for individual pharmaceutical donors to guide their funding towards specific drugs. We see most exposed drugs prostate cancer (namely Xtandi and Zytiga), idiopathic pulmonary fibrosis (Roche's Esbriet and Boehringer's Ofev) >> colorectal cancer (Bayer's Stivarga) > lung cancer (AZN's Tagrisso, Roche's Tarceva). This additional novel dynamic is additive to our previous concerns for high priced oral drugs due to growing evidence of PBM induced formulary management and growth in high deductible plans in the commercial segment report *Bark, Bite, Bounce?: Can Pharma Be a Winner in Trump's America?* (dated 23 Feb 2017). We prefer BUY rated BMY and LLY among the US majors. We prefer BUY rated GSK, AZN, Roche and Bayer among the EU majors.

- **What's new?** Each $1m industry donation to a charitable foundation to enable Medicare patients Xtandi access or similar high priced drugs has the potential to generate up to $21m for the sponsor company, funded by the US Government**.** The industry has recently diminished funding of independent foundations designed to increase Medicare Part D patient access to high priced drugs given the ongoing investigations of several company's activities by the DoJ and OIG under Federal Kickback Provisions. Companies under subpoena since 2016 include Pfizer, Valeant, Jazz, Celgene, Ariad, Gilead and Biogen. We see the greatest legal risk to Foundations funding therapeutic areas with few branded therapeutic options. In the absence of co-pay support for Medicare patients from Foundations, we anticipate significant revenue head-winds as sponsors either provide free drugs or lose up to 1/3 of eligible patients.

- **What's next?** We anticipate rulings from on-going investigations over the next 12-24 months to determine industry policy. The most likely outcome is that industry will no longer fund disease specific funds with few branded therapeutic options, limiting the future growth potential of several important categories, especially prostate and IPF. We continue to see Medicare part D exposure as an overall market for risk as outlined in our recent sector Analysis of revenue and scrip trends and overall company revenue impact is summarized in this report.

Most / Least Preferred

Figure 1. AstraZeneca and Roche are our most favoured large-cap stocks in Europe, LLY and BMY in the US

	Rating	Price Target	Investment Thesis	Immuno-oncology	"Shrink, Smarten, Spin"	Biologics	Vaccines	Diagnostics	Consumer Health	Emerging Markets	Biosimilars	Epigenetics	Animal Health
AstraZeneca	Buy	£60	Shrink research. De-equitisation growth drivers	✓✓✓	✓✓	✓	✓	✓		✓✓		✓	
Roche	Buy	CHF 280	Innovation, immunotherapy	✓✓✓	✓✓	✓✓✓		✓✓✓		✓✓		✓	
Bayer	Buy	€120	Xarelto, Emerging Markets		✓	✓✓		✓	✓✓✓	✓✓✓		✓	✓
Eli Lilly	Buy	$100	Pipeline, base incl. Alimta, EM	✓	✓✓✓	✓✓✓				✓✓		✓	✓✓✓
Bristol Myers-Squibb	Buy	$55	Immunotherapy	✓✓✓	✓✓✓	✓✓				✓		✓	
Merck KGaA	Buy	€116	Pipeline, Life Science Transformation	✓	✓	✓✓			✓	✓✓	✓		
GlaxoSmithKline	Buy	£18	Dividend covers pipeline	✓	✓✓	✓	✓✓✓		✓✓✓	✓✓		✓✓✓	
Sanofi	Neutral	€80	Return to sustainable growth		✓✓✓	✓✓	✓✓✓		✓✓✓	✓✓✓	✓		✓✓✓
Pfizer	Neutral	$38	Cost, WC De-equitisation	✓	✓✓✓	✓✓	✓✓		✓	✓✓	✓✓	✓✓	
Merck & Co	Neutral	$65	Cost, WC reduction pipeline	✓✓	✓✓	✓	✓✓✓			✓✓	✓	✓	✓✓✓
AbbVie	Neutral	US$60	Humira Biosimilar Risks	✓	✓	✓✓✓				✓		✓✓	
Novo Nordisk	Neutral	DKK 250	Emerging markets, diabetes		✓	✓✓✓				✓✓✓			
Novartis	Neutral	CHF 79	Innovation vs LOE. Restructuring	✓✓	✓✓	✓			✓✓	✓✓	✓✓✓	✓✓	

Source: Citi Research

Valuation

Figure 2. Pharma Valuation

Company	RIC	Analyst	Currency	Current price	Market cap ($bn)	Rating/Risk	Target			2018E multiple		2018-23E CAGR		2018E div yield
							Price	% upside	ETR	PE	EV/EBITDA	Sales	EPS	
US Large Cap Pharma														
AbbVie	ABBV.N	Andrew Baum, MD	USD	66.7	106.1	Neutral	60.0	-10%	-6%	10.8	10.1	-1.6%	-2.2%	4.6%
Bristol Myers	BMY.N	Andrew Baum, MD	USD	55.1	90.8	Buy	55.0	0%	3%	17.9	15.1	4.2%	10.2%	3.0%
Eli Lilly	LLY.N	Andrew Baum, MD	USD	80.3	88.6	Buy	92.0	15%	17%	18.1	12.8	6.1%	12.6%	2.7%
Merck	MRK.N	Andrew Baum, MD	USD	63.5	173.7	Neutral	65.0	2%	5%	15.4	10.4	0.4%	2.9%	3.1%
Pfizer	PFE.N	Andrew Baum, MD	USD	33.1	197.2	Sell	31.0	-6%	-3%	12.1	9.7	1.1%	3.5%	4.0%
US Large-cap Pharma (mkt-cap wt avg)										*14.4*	*11.1*	*2%*	*5%*	*4%*
European Large Cap Pharma														
AstraZeneca	AZN.L	Andrew Baum, MD	GBP	51.9	84.7	Buy	60.0	16%	20%	14.7	10.9	11.1%	17.8%	4.2%
Bayer	BAYGN.DE	Peter Verdult, CFA	EUR	116.1	104.9	Buy	130.0	12%	14%	13.1	9.2	4.9%	9.1%	2.8%
GlaxoSmithKline	GSK.L	Andrew Baum, MD	GBP	1,658.5	105.1	Buy	18.0	9%	13%	14.9	10.4	4.9%	8.2%	4.8%
Novo-Nordisk	NOVOB.CO	Peter Verdult, CFA	DKK	274.4	100.8	Neutral	250.0	-9%	-6%	16.8	9.8	6.0%	9.5%	3.0%
Novartis	NOVN.S	Andrew Baum, MD	CHF	80.5	210.4	Neutral	79.0	-2%	2%	14.5	13.4	3.7%	8.0%	3.7%
Roche	ROG.S	Andrew Baum, MD	CHF	269.5	232.4	Buy	280.0	4%	7%	15.2	10.3	3.8%	4.5%	3.5%
Sanofi	SASY.PA	Peter Verdult, CFA	EUR	93.0	127.6	Neutral	80.0	-14%	-11%	15.3	10.4	4.9%	6.5%	3.4%
EU Large-cap Pharma (mkt-cap wt avg)										*14.9*	*10.9*	*5%*	*8%*	*4%*
European Mid Cap Pharma														
Hikma	HIK.L	Peter Verdult, CFA	GBP	17.4	5.4	Neutral	19.5	12%	14%	12.0	7.1	4.6%	11.4%	1.9%
Merck	MRCG.DE	Peter Verdult, CFA	EUR	113.2	53.8	Buy	116.0	2%	4%	16.5	13.0	5.1%	8.8%	1.2%
UCB	UCB.BE	Peter Verdult, CFA	EUR	77.1	16.4	Buy	98.0	27%	29%	16.0	10.2	5.6%	14.6%	1.6%
EU Mid-cap Pharma (mkt-cap wt avg)										*16.1*	*11.9*	*5%*	*10%*	*1%*
Global Large-cap Pharma (mkt-cap wt avg)										*14.7*	*11.0*	*4%*	*7%*	*4%*

Source: Powered by dataCentral. Priced 15th May (at 20:00 GMT)

Summary and Investment Conclusion.

Our recent in depth industry analysis *Bark, Bite, Bounce?: Can Pharma Be a Winner in Trump's America?* (dated 23 Feb 2017) concluded that the risk of adverse market forces on the outlook for pharmaceutical companies was likely far more significant than the risk of adverse legislative action on drug pricing.

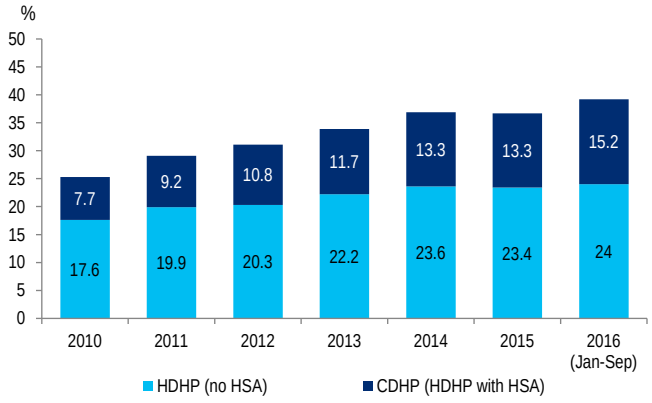
We highlight the damaging impact of the rise of high deductible plans in the commercial segment and the broadening and deepening of PBM formulary management tools such as restrictive formularies and prior authorizations in the Medicare segment. We noted the CVS decision to withdraw NVS's Tasigna from their national formulary, despite its gold standard status. The growing density of small molecule ALK inhibitors, CDK4/6 inhibitors, PARP inhibitors as well as many other classes provides a fertile environment for PBM's to secure rebates in exchange for volume, even within protected categories of Medicare Part D formularies.

The rise of 340B designate hospitals as the major provider of outpatient oncology drugs (c. 50%) has driven significant increase in mandatory pharmaceutical rebates for both Medicare and commercial patients for specialty pharmaceutical delivered under both a pharmacy and a medical benefit.

We identified the growing use of white bagging fuelled by the increasing importance of 340B designate pharmacies extending the reach of PBM's into therapeutic areas previously beyond their control including haemophilia, growth hormone and supportive cancer injectable oncology products

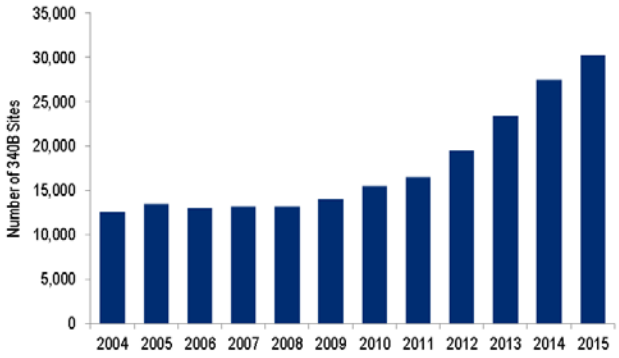
On top of these dynamics we can now add the potential significant negative impact of the diminished ability of the industry to alleviate Medicare out of pocket spends through financial donations to charitable foundations. While we of course noted the intensification of DOJ/OIG activity in relation to charitable foundations during 2016, we perhaps underestimated the commercial impact.

Figure 3. Percentage of under 65s enrolled in a High Deductible Health Plan (HDHP) approaching 40%



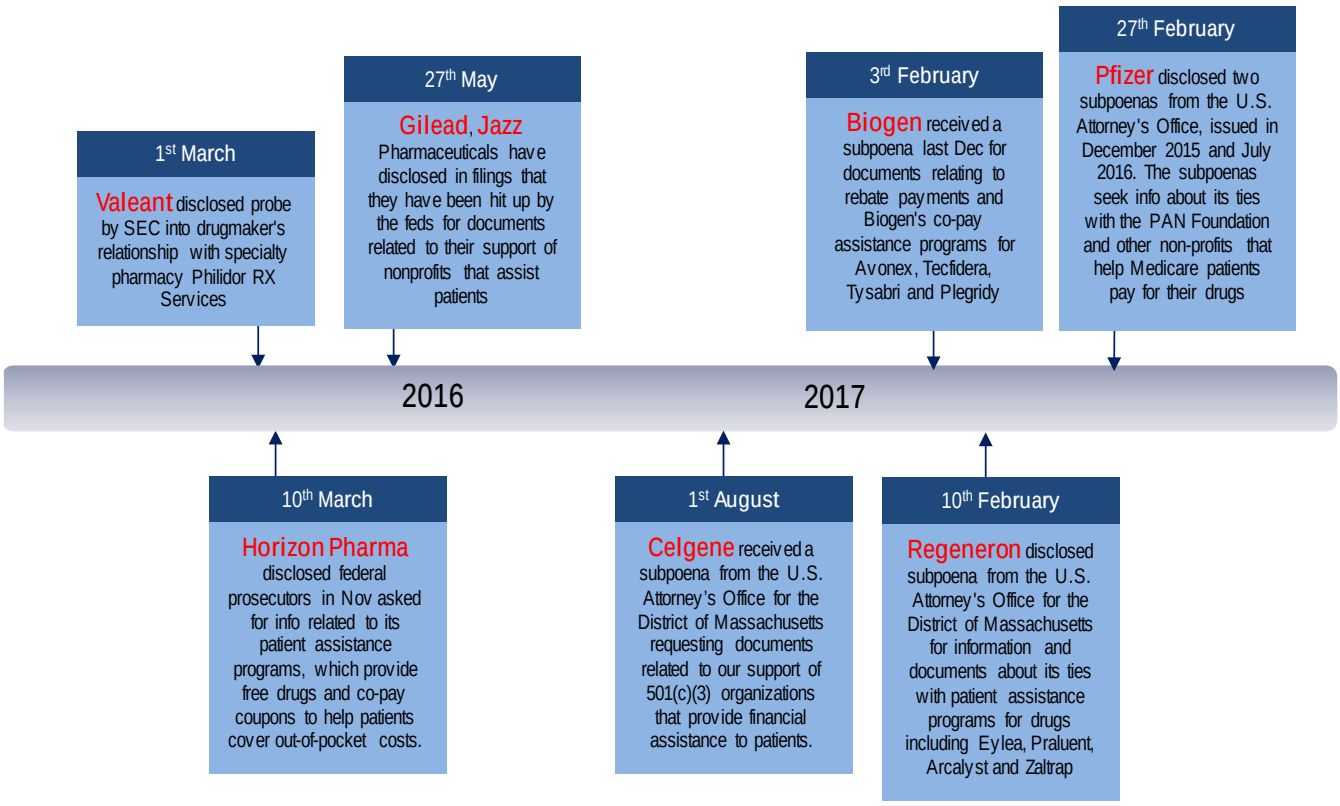
Source: National Health Interview Survey, Citi Research

Figure 4. Exponential growth in number of 340B sites fueled by attractive drug purchase/reimbursement economics



Source: Avalere Health analysis of the 340B database, Citi Research

Figure 5. DOJ and OIG investigations into the use of PAP and Charitable donations have intensified since 2Q 2016



Source: Citi Research, Company Reports

How do Independent Foundations Work? Many Medicare patients are entirely reliant on external funding to obtain their medications given the $4,950+ out of pocket spend for high price specialty pharmaceuticals covered under Medicare Part D, as well as the 5% co-pay once the patients enters the catastrophic coverage period. PAN (Patient Assistance Network) foundation, the largest of the independent patient assistance foundations receives direct financial funding from industry sponsors used to assist OOP (Out-of-Pocket) expenses. The sponsor contributes to one of 60 disease specific funds within PAN. From these funds, individual $10k patient grants are allocated to patients that meet the eligibility requirements (up to 500 percent of Federal Poverty level (up to $140k per annum for one person household), accounting for at least 20 million Medicare patients. Individual disease funds are opening and closing at all times due to the ebb and flow of donations. ***Each $1m industry donation that is used to aid patients with their access to Xtandi or similar high priced drugs has the potential to generate up to $21m for the sponsor company.***

Donations from Industry slowing. Under anti-kickback statutes, pharmaceuticals sponsors are prohibited from directly or indirectly alleviating patient out of pocket spend for Medicare and Medicaid programs. Numerous regulations preclude the sponsors from directing their donation to a specific drug. These conditions have been significantly tightened over the last 3 years. Several funds are now not open all year compared with previously. Some manufacturers are only donating if the charity meets 33% of the public support test. Successful prosecution or settlement

in the aforementioned DoJ/ OIG investigations could lead to further material reduction in foundation funding by the industry with a significant negative impact on anticipated sales for high price Medicare Part D exposed specialty pharmaceuticals.

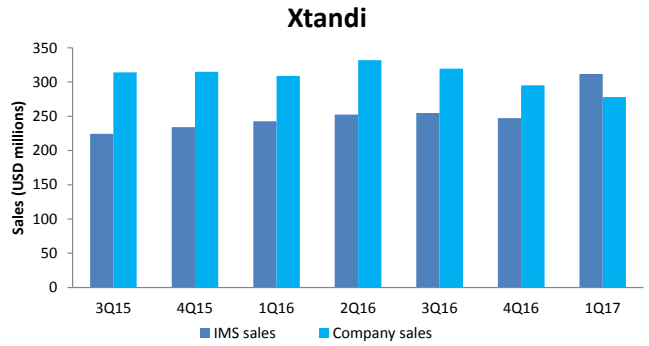
Pfizer reported 13% demand growth in the US for Xtandi, acquired through the $14bn Medivation transaction in 2016. However, the reported 1Q 2017 US revenue growth reflects a c.10% QoQ reduction. Pfizer has described that the on-going DoJ OIG investigations have led to a significant reduction in industry donations to independent not-for-profit charitable foundations designed to alleviate Medicare patient co-pays for specialty drugs. Prior to the acquisition of Medivation by Pfizer, we anticipate that Zytiga's sponsor was likely the largest donor to Prostate related foundations such as Patient Access Network (PAN) Foundation. Pfizer indicated that the reduction in funding through charitable mechanisms has forced both manufacturer to provide Xtandi and Zytiga for free through their respective patient assistance programs. We calculate that up to 30% of patients on Xtandi may now be receiving free drug through Pfizer's patient assistance program. We interpret the comments on Ian Reid, PFE's CEO on the conference call that the situation has stabilized and is beginning to improve as suggestive that PFE has stepped into the void left by Zytiga's sponsor and is actively contributing to Foundation's despite the on-going investigations. Assuming all this donation is used to cover co-pays for Medicare Part D drugs, the net financial benefit of the contributions alone could be as much as $800m per annum in Medicare Part D revenues that would likely remain unrealised in the absence of the industries co-pay support – an impressive financial return indeed.

Figure 6. Notable Charitable Funding by Pfizer from 1Q 2016 to 3Q 2016.

Oranisations	Contributions ($)
American Academy of Pediatrics (Immunisation, ADHD)	2,110,000
American College of Physicians (Immunisation)	1,171,068
Assistance Found Inc (RCC)	2,000,000
Avon Products Foundation Inc (Breast Cancer)	750,000
Conqure Cancer Foundation ASCO	1,000,000
Healthwell Foundation (NSCLC, CML)	750,000
Immunization Action Coalition (Immunisation)	1,000,000
PAN Foundation (Acromegaly, RCC, Arrhythmia)	10,950,000
Patient Advocate Foundation (Breast Cancer)	3,025,000
Task Force for Global Health Inc (Trachoma)	5,300,000
Assistance Fund Inc (RCC, RA)	1,500,000
Sub-Total	$29.6m
Total Charitable Donations	$82.2m

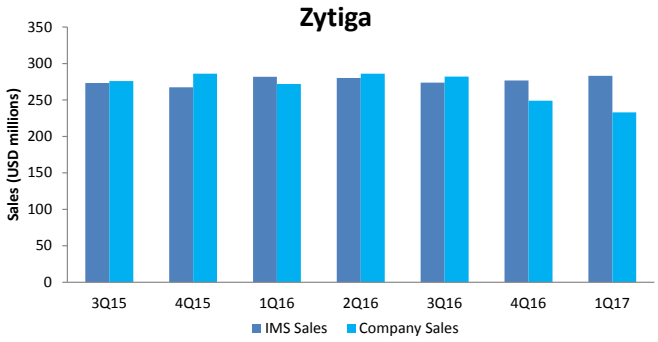
Source: Citi Research, Company Report

Figure 7. Xtandi sales reported by IMS and Company declining since 2Q16



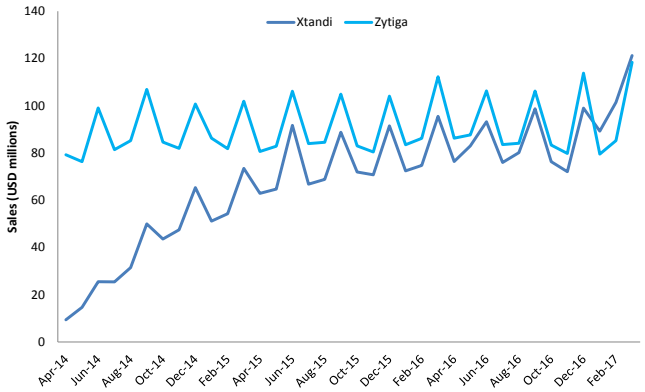
Source: Citi Research, Company data, IMS health

Figure 8. Zytiga sales reported by IMS and Company declining since 2Q16



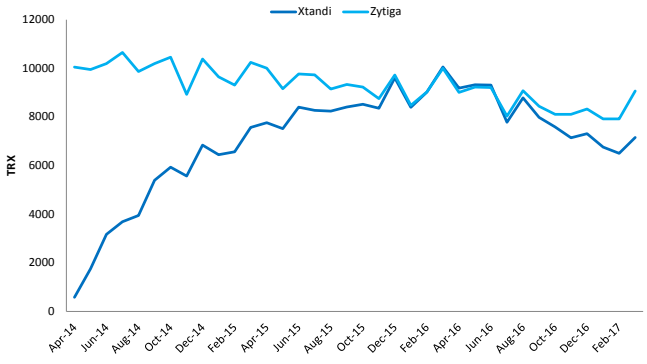
Source: Citi Research, Company data, IMS health

Figure 9. Monthly sales from IMS for Xtandi and Zytiga



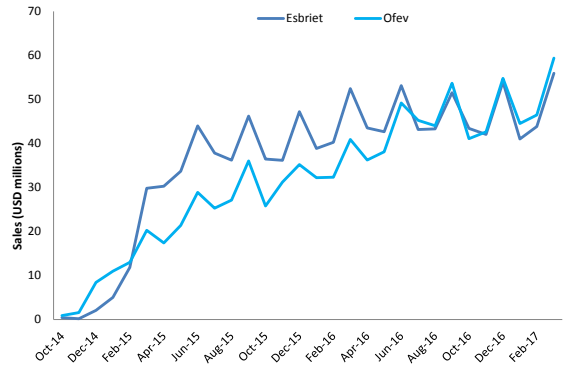
Source: Citi Research, IMS health

Figure 10. Xtandi and Zytiga Scripts Declining



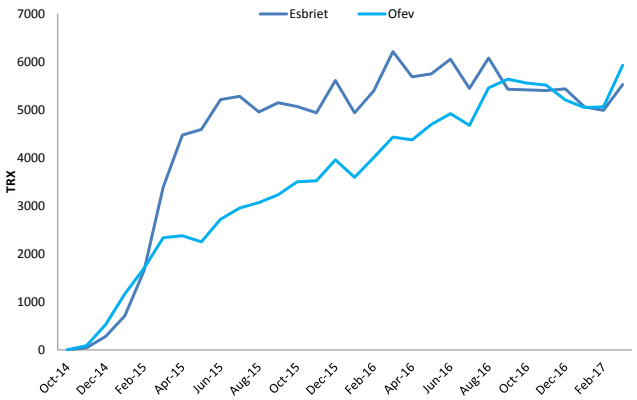
Source: Citi Research, IMS health

Figure 11. Monthly sales from IMS for Esbriet and Ofev



Source: Citi Research, IMS health

Figure 12. Esbriet and Ofev Scripts have decline or plateaued since 2Q1

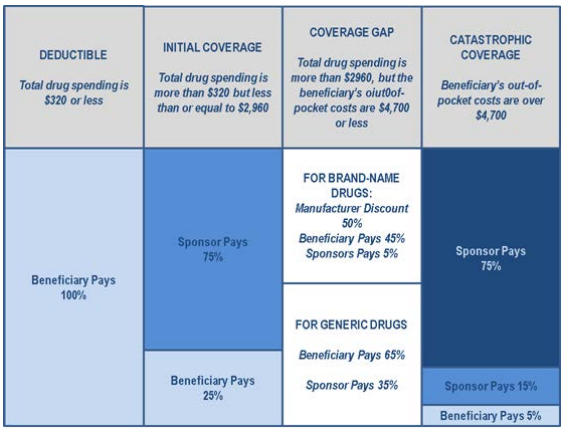


Source: Citi Research, IMS health

The dynamics of Medicare Part D Coverage. For drugs covered under Medicare part D, patients have to pay a $320 deductible and then are liable for co-pays. After the first $2960, the patient falls into the donut hole and has to cover 45% - 65% of the total cost of therapy until he reaches $4,700 when catastrophic coverage is triggered and Medicare pays in full for the cost of therapy. Industry is unable to fund

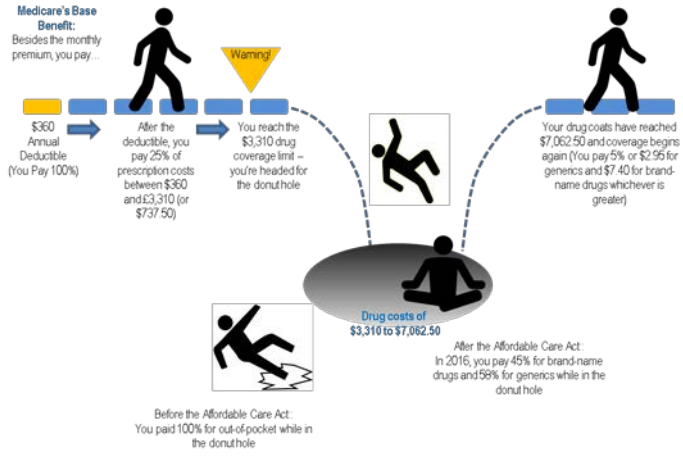
directly or with vouchers the out of pocket contributions for drugs covered under Medicare due to anti-kickback statutes. Medicare patients unable or unwilling to pay the c.$5,000 out of pocket expense are therefore unable to obtain their drugs despite their Medicare coverage. The industry has extensively used independent third party charitable foundations to assist with the out of pocket spend of patients receiving their drugs as part of a Medicare Part D drug benefit. Initial Medicare co-pays for specialty drugs run from 20% - 30% translating into over $2,000 per month for drugs such as Xtandi, and even post reaching catastrophic coverage, there is a continued co-pay of c.$500 per month for the patient.

Figure 13. The standard of the Medicare Part D drug benefit



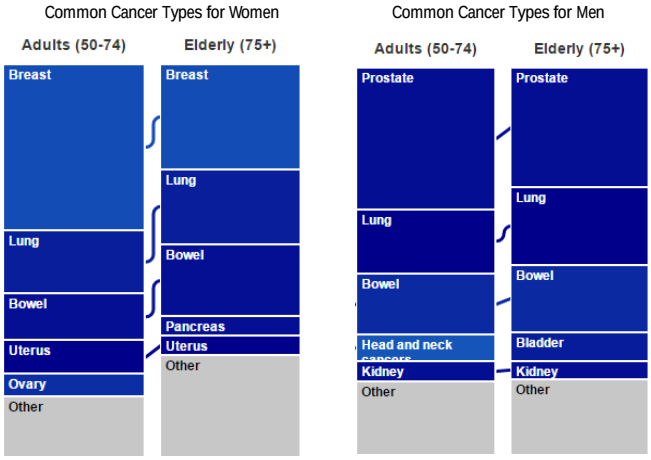
Source: Citi Research

Figure 14. Majority of Medicare patients dependent on Foundations to subsidize $4900 out of pocket spend + 5% co-pays for Part D specialty pharmaceuticals.



Source: Citi Research

Figure 15. Prostate, Lung and Breast Cancers are over represented in elder population.



Source: Citi Research, Cancer Research

Why Prostate Cancer? We believe that the impact is most visible for Prostate cancer drugs given the over-representation of patients receiving their drugs under Medicare, given the demographic of the disease. Importantly the high list prices of for Zytiga and Xtandi respectively carry the maximum $4,900 out of pocket spend within the first months- increasing the financial burden for the patients. Finally, we anticipate that the industry nervousness over donations to prostate cancer specific indications has increased significantly given there are only two significant branded drugs within the prostate cancer category making the sponsors particularly vulnerable to claims that contributions to Prostate Cancer specific foundations are effectively a kickback to benefit future drug revenues.

Who else is impacted? We looked for therapeutic areas with similar risk profiles as outlined above for prostate cancer. We highlight IPF (idiopathic pulmonary fibrosis), and multiple myeloma. It comes as little surprise that the major financial donors for IPF Disease Funds are Genentech and Boehringer.

Part B Medicare drugs less impacted. We believe the impact of the DOJ/OIG dynamic to be most visible on drugs covered under a part D rather than a part B benefit given the availability of supplemental coverage through Medigap, etc. to diminish the co-pay burden for the patient. These mechanisms are not accessible for drugs received under Medicare Part B.

The Future. We anticipate that foundations will not disappear. Instead the industry will be forced to abandon narrow disease specific foundations, especially where there are few treatment alternatives. Instead we see industry contributing to foundations with a broader disease mandates. This will diminish legislative risk but limit the ability of industry sponsors to target their donations to alleviate the co-pay burden for drugs for which they directly stand to benefit. Under this scenario, we anticipate a much slowed growth trajectory for therapeutic areas such as prostate cancer and IPF. This dynamic would increase the risk that the recent acquisitions of Medivation by Pfizer and Intermune by Roche have destroyed rather than created value.

Companies mentioned:

(ABBV.N; US$66.06; 2; 12 May 17; 16:00); (AGN.N; US$230.88; 1; 12 May 17; 16:00); (AZN.L; £51.94; 1; 15 May 17; 16:30); (BAYGn.DE; €116.05; 1; 15 May 17; 17:30); (BIIB.O; US$254.84; 1; 12 May 17; 16:00); (BMY.N; US$55.03; 1; 12 May 17; 16:00); (VRX.N; US$13.59; Not Rated; 12 May 17; 16:00); (CELG.O; US$119.32; 1; 12 May 17; 16:00); (GILD.O; US$66.06; 2; 12 May 17; 16:00); (GSK.L; £16.59; 1; 15 May 17; 16:30); (HIK.L; £17.38; 2; 15 May 17; 16:30); (HZNP.O; US$10.19; 1; 12 May 17; 16:00); (JAZZ.O; US$153.79; 1; 12 May 17; 16:00); (LLY.N; US$80.19; 1; 12 May 17; 16:00); (MRCG.DE; €113.20; 1; 15 May 17; 17:30); (MRK.N; US$63.57; 2; 12 May 17; 16:00); (NOVN.S; SFr80.45; 2; 15 May 17; 17:30); (NOVOb.CO; Dkr274.40; 2; 15 May 17; 17:00); (PFE.N; US$33.01; 2; 12 May 17; 16:00); (REGN.O; US$442.05; 1; 12 May 17; 16:00); (ROG.S; SFr269.50; 1; 15 May 17; 17:30); (SASY.PA; €92.97; 2; 15 May 17; 17:30); (UCB.BR; €77.11; 1; 15 May 17; 17:30)

Medivation, Intermune and Boehringer are private or no longer listed.

Appendix A-1

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tctMD/the heart beat

FEATURE

'Outrageous' $225,000 per Year List Price for Tafamidis Draws Outcry

Pfizer is "gouging" payers, say researchers, noting that elderly patients have out-of-pocket costs of $1,000 to $2,000 a month.

By Michael O'Riordan January 10, 2020

Several heart failure physicians, specifically those who treat patients with cardiomyopathy caused by transthyretin amyloidosis (ATTR-CM), are calling attention to the extraordinarily high price of tafamidis and tafamidis meglumine (Vyndamax and Vyndaqel; Pfizer), both of which received orphan drug designation and were approved by the US Food and Drug Administration in 2019.

PFE000668

With a list price of $225,000 per year, tafamidis is the most expensive cardiovascular drug on the market. Mathew Maurer, MD (Columbia University Irving Medical Center, New York, NY), who published his views along with Jerry Gurwitz, MD (University of Massachusetts Medical School, Worcester), January 8, 2020, in *JAMA Cardiology*, told TCTMD the high prices for tafamidis "are not justified and appear to be a particularly egregious example of price gouging."

The out-of-pocket costs for most patients are difficult to pin down given rebates and subsidies, but Maurer said his patients pay roughly $1,000 to $2,000 each month if they don't receive additional financial support. "It's anxiety provoking," he said. "If nobody believes that, come to my clinic where I have to sit with patients who are worried how they're going to get it, if it's going to be sustainable, and if it's going to work out. That's a shame if you're sick."

> *"It's anxiety provoking. If nobody believes that, come to my clinic where I have to sit with patients who are worried how they're going to get it."*
> ***MATHEW MAURER***

Rodney Falk, MD (Brigham and Women's Hospital, Boston, MA), who runs a specialized cardiac amyloidosis program, called the list price "outrageous."

"Almost two-thirds of our patients have an initial monthly copay of more than $1,000 per month with Medicare," he told TCTMD. "Those with very low incomes—those are people who can usually get some type of subsidy. But for the average person on an average income, $1,000 is still a lot of money and they can't get any subsidies."

One patient with ATTR-CM, said Falk, ran the numbers and weighed the financial impact with his current symptoms, and despite his life-threatening, progressive condition ultimately decided against tafamidis. "He went out and bought himself a brand-new pickup truck," Falk recalled, "because he said that's the drug cost for the first 2 years and he might as well enjoy himself."

What Is ATTR-CM?

ATTR-CM is inherited as an autosomal dominant trait caused by mutations in the transthyretin gene (*TTR*) or by the deposition of wild-type transthyretin proteins. Tafamidis slows the progression of ATTR-CM—it doesn't cure it—but experts have cautioned that a delayed diagnosis typically leads to worse prognosis. The average life expectancy from the time of diagnosis until death is roughly 2 to 6 years.

That quarter-of-a-million dollar per year price tag might be justified if ATTR-CM was an extremely rare condition, but experts say that just isn't the case. To TCTMD, Ronald Witteles, MD (Stanford University Medical Center, CA), who is co-director of the amyloid program at his institution, said he was "surprised, and not happily so" when Pfizer announced the price of tafamidis following the FDA approval.

"It was priced like a drug is typically priced for a truly rare disease, which this simply isn't," he said, adding that if there were 1,000 people or fewer in the country with ATTR-CM, the inflated price tag might be expected. "It's not common like high blood pressure or coronary artery disease, but it is definitely not truly rare."

Like Maurer and Gurwitz, Witteles pointed out that Medicare Part D patients in the coverage gap can be responsible for up to 5% of the drug costs. "For a drug that's $1,000 a year that isn't too big a burden," he said. "For a drug that's $225,000 a year, that's a very different story."

Maurer said the prevalence of ATTR-CM is not truly known, noting that there are few population-based epidemiological studies documenting the disease. Pfizer estimates the prevalence of ATTR-CM to be approximately 100,000 people in the United States and that approximately 4 to 5% of people are diagnosed, but Maurer and Gurwitz highlight one study suggesting a prevalence of 13% among patients with heart failure with preserved ejection fraction (HFpEF) and increased wall thickness.

> *"It was priced like a drug is typically priced for a truly rare disease, which this simply isn't."*
> ***Ronald Witteles***

"It's much more common than we recognized a decade ago," said Falk. "Every single major amyloid center has seen an enormous surge in TTR amyloid, particularly wild-type TTR amyloidosis. Many people believe it's responsible for about 5% to 10% of older patients with heart failure with preserved ejection fraction, which is an awful lot of patients."

In the past, said Maurer, people simply never lived to an age when they'd develop ATTR-CM, a disease that strikes individuals 65 years and older. Also aiding in the increased number of cases is the development of a noninvasive diagnostic strategy, as opposed to a previously required heart biopsy, that uses technetium-labeled bone scintigraphy along with blood testing for monoclonal proteins.

Maurer said that awareness around ATTR-CM is also growing because physicians recognize the deadly nature of the disease. "It's not an innocent bystander," he said. "It's clear that if you find it and treat someone you can help them live longer and feel better, or at least feel less worse."

In the pivotal ATTR-ACT study, led by Maurer and published in the *New England Journal of Medicine*, researchers showed that tafamidis reduced the risk of all-cause mortality and cardiovascular hospitalizations at 30 months when compared with placebo . In terms of symptoms, tafamidis treatment led to improvements in the 6-minute walk test and various quality-of-life scores.

To TCTMD, Gurwitz praised Maurer, noting that he's been on the forefront of research leading to breakthroughs in the diagnosis of ATTR-CM. In their article, the two state that if the prevalence of any disease or condition exceeds 200,000 persons, the orphan drug designation and its market exclusivity should be revisited.

"How would the drug be priced if [ATTR-CM] was a more prevalent condition?" asked Gurwitz. "We don't know. It could have been

priced at the same level, who knows, because pricing isn't rationale or value-based in any way."

In a statement, a Pfizer spokesperson told TCTMD the company believes the price of tafamidis is in line with the value the drug brings to patients and society and noted that the list price is not what patients pay. Pfizer also agreed that it's difficult to measure the true prevalence of ATTR-CM.

"While physicians may be more likely to diagnose ATTR-CM now that there is an approved treatment, it remains to be seen at what rate this will continue in the coming months and years," the statement reads. "As part of our commitment to the ATTR-CM community, we intend to conduct two epidemiology studies to help improve our understanding of the prevalence of the disease. If it turns out this is not a rare disease, we will reevaluate the price accordingly."

Subset of the HFpEF Population

Speaking to broader issues, Maurer said researchers have spent 25 years trying to identify the pathophysiology of HFpEF, or diastolic HF. Countless trials testing agents successful in systolic HF have not panned out, but there has been some success in breaking HFpEF patients into different subgroups. ATTR-CM is one of those subgroups, and dedicated research looking only at these patients has led to successful treatment with tafamidis. However, there are a number of other HFpEF subgroups, and if future agents also receive orphan-status designation cost is going to be a major factor.

"How are we going to afford this?" asked Maurer. "If we're taking what is a common condition and making it into a rare disease because we've found a small subgroup, it sounds to me like this is unsustainable. Trust me, I'm thrilled that this drug works. I have hundreds of patients and I'm grateful to give it to them. And I want to be transparent—I think the scientist who developed this, Jeffery Kelly, is brilliant. In my opinion he deserves a Nobel Prize. I don't even fault the drug company per se. I want them to get their due, but I don't think we're considering the societal issues."

> *"There's no reason why Pfizer couldn't swallow the research costs because of the huge profits they're making off other drugs."*
> ***Ronald Falk***

Maurer criticized the current system, noting that the US government is unable to set drug prices for Medicare patients and is suffering the consequences for it.

"I think it's a little bit ludicrous—I love my patients and I think they should get the drug—but to spend a quarter of a million dollars every year on patients who are 80 years of age? Not to be disrespectful to them, but it's not sustainable," he stressed.

To TCTMD, Falk said the traditional response from pharmaceutical companies is that the high price is justified given the enormous outlay in research and development.

"I don't buy that argument," he said. "There's no reason why Pfizer couldn't swallow the research costs because of the huge profits they're making off other drugs. Secondly, we've prescribed it to 100 patients this year. If you reckon $225,000 per year, that's $22 million that we put into Pfizer. Multiply that by a couple of years, that's $40 or $50 million and that's from one center. They've made their money back, unquestionably."

Moreover, Pfizer isn't a small company making a single drug. Pharmaceutical companies are frequently touting their commitment to patient care, and this is an opportunity for Pfizer to put their money where their mouth is, Falk said. They could take a loss on tafamidis and earn the money back with drugs for more common conditions.

"They could show themselves to be, I won't say altruistic, but they could back up what they're actually saying," said Falk. "They say, 'We want to help patients with these [rare] diseases' and so on and so forth. They could do that."

In cardiology, the makers of the PCSK9 inhibitors faced significant backlash when they initially priced alirocumab (Praluent;

Sanofi/Regeneron) and evolocumab (Repatha; Amgen) at nearly $15,000 per year, although that drug class is for a much more common disease affecting a significantly larger number of patients. The companies eventually cut their prices—slashing the costs by roughly 60%—when uptake stalled.

"The thinking is, if you lower the price, the drugs will be prescribed more," said Gurwitz. "Perhaps that might happen here, but I'm not so sure. This isn't the same scenario."

Implications for Research

In addition to the burden for patients and payers, the high cost of tafamidis also has research implications, according to Gurwitz and Maurer. Given the price tag, Pfizer essentially blocks future clinical trials that could use tafamidis as an active comparator, which Maurer said is wrong. Tafamidis is the current gold standard of care in ATTR-CM so future studies should be compared on top of or against tafamidis and not placebo. Maurer is the site principal investigator of several phase III clinical trials about to launch.

"Each one of those trials should, in theory, offer tafamidis to the control group," Maurer told TCTMD. "That's what should happen scientifically. That's important for what I as scientist want to know, as do patients. Is this new drug, when added on top of tafamidis or compared with tafamidis better or worse?"

For that to happen, competing companies would need to buy tafamidis from Pfizer at the list price, which ups the cost of a clinical trial by a couple hundred million dollars depending on its size and duration. "We're forced to do studies in unideal circumstances," said Maurer. "And this prevents patients from getting the best drug the fastest."

As a solution, Maurer believes the US government could get involved by paying for tafamidis in active comparator studies. As part of that deal, they could force companies to keep their prices much lower than Pfizer's $225,000 price tag if the new drug was successful in clinical testing, he suggested.

Two agents, inotersen (Tegsedi; Akcea) and patisiran (Onpattro; Alnylam), both of which are approved as orphan agents for the treatment of the much-rarer hereditary amyloidosis, a disease the

primarily affects the nervous system, will be tested in patients with ATTR-CM. Patisiran currently has a list price of $350,000 per year, while inotersen costs $450,000. An investigational small molecule (AG10, Eidos Therapeutics) that stabilizes TTR is also being developed for and tested in cardiomyopathy and polyneuropathy. AG10 has already been designated an orphan drug by the FDA.

Disclosures

Gurwitz reports serving on the pharmacy and therapeutics committee from United Healthcare outside the submitted work.

Maurer reported grants, personal fees, and nonfinancial support from Pfizer and Alnylam, grants and personal fees from Eidos and Akcea, and grants from the National Heart, Lung, and Blood Institute and the National Institute on Aging.

Witteles reports grants from Pfizer, Alnylam, and Eidos and personal fees from Pfizer and Alnylam.

Falk reports consulting fees from Ionis Pharmaceuticals and Alnylam Pharmaceuticals and research funding from GlaxoSmithKline.

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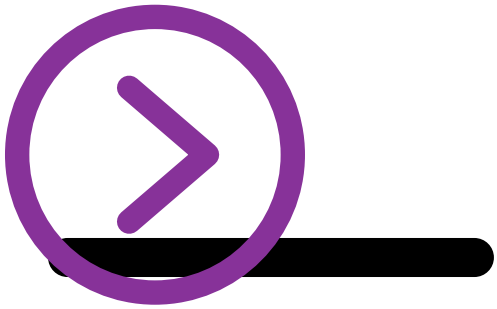

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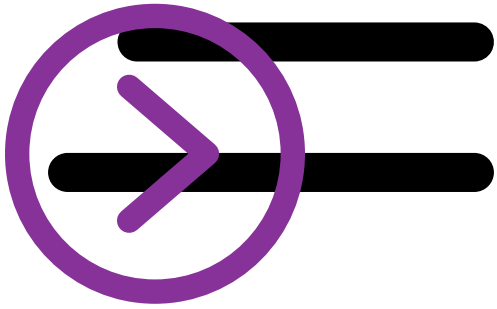

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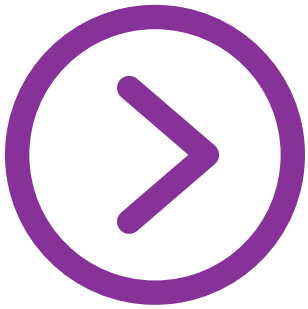

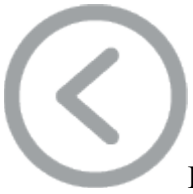

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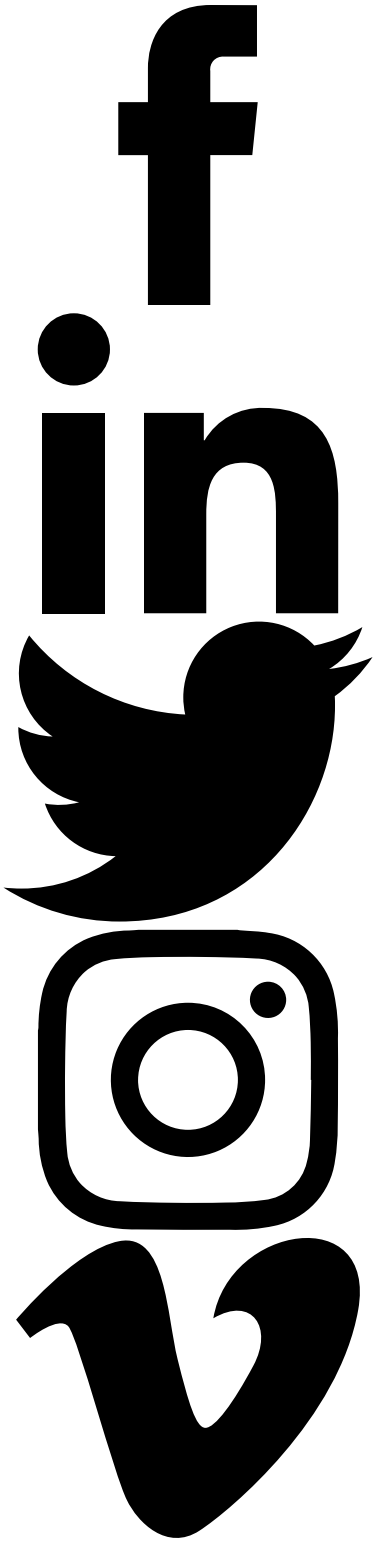

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Headquarters: The Assistance Fund
4700 Millenia Blvd., Suite 410
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Washington, DC Satellite Office:
655 15th St. NW, Suite 502
Washington, DC 20005

The Assistance Fund Opens New Program for Hereditary (ATTR) Amyloidosis

Authored by:

TAF Author

2 years ago

FOR IMMEDIATE RELEASE

The Assistance Fund Launches New Program to Provide Financial Support to Individuals with Hereditary (ATTR) Amyloidosis

ORLANDO, Fla., August 20, 2018 — The Assistance Fund, an independent charitable patient assistance foundation that helps patients and families facing high medical out-of-pocket costs, launched a new financial assistance program to provide support for individuals with Hereditary (ATTR) Amyloidosis. The program covers out-of-pocket medical expenses, including medication copays, health insurance premiums, deductibles, coinsurance and incidental medical expenses for eligible individuals.

“It is with great excitement that we open this new financial assistance program so that patients with Hereditary (ATTR) Amyloidosis can pursue treatment without being burdened by undue financial stress,” said The Assistance Fund President and CEO Mark P. McGreevy.

“Hereditary Amyloidosis has a huge impact on families, in which generations may be affected by the disease,” said Isabelle Lousada, President and CEO of the Amyloidosis Research Consortium. “As the disease progresses, patients experience a considerable impact on their quality of life and ability to work, as well as their social and emotional well-being. New treatments that can slow progression and minimize the effect of symptoms offer real hope to patients.”

Hereditary (ATTR) Amyloidosis is a condition that affects organ tissue structure and function when amyloid, an abnormal protein, is deposited in multiple organs where it should not be, most often in tissues of the heart, kidneys and nervous system.[1] Symptoms can vary broadly among patients and may include heart palpitations and abnormal heart rhythms, a loss of sensation in the extremities, digestive issues, swelling, and many other issues.[2]

"Finally, patients have hope for treating this disease," said Mary O'Donnell, President and CEO of the Amyloidosis Foundation. "The Assistance Fund's financial assistance program for Hereditary (ATTR) Amyloidosis will provide extremely important support for patients who may otherwise be unable to seek treatment due to high out-of-pocket costs."

To learn more or determine eligibility for financial support from The Assistance Fund, individuals should visit tafcares.org or call 855-512-2801 to speak with a patient advocate.

A list of all the programs available at The Assistance Fund can be found on the website tafcares.org.

About The Assistance Fund

The Assistance Fund is an independent charitable patient assistance foundation that helps patients and families facing high medical out-of-pocket costs by providing financial assistance for their copayments, coinsurance, deductibles and other health-related expenses. The Assistance Fund currently manages more than 40 programs – each of which covers the FDA-approved medications that treat a specific disease. Since its founding in 2009, The Assistance Fund has helped more than 73,000 adults and children access the medicines they need to stay healthy or manage a chronic condition. To learn more about The Assistance Fund, or for information on how to donate, please visit tafcares.org.

Media Contact
Dan Boyle
Orangefiery
(818) 209-1692
dan@orangefiery.com

References

1- "Hereditary amyloidosis" National Institutes of Health, National Center for Advancing Translational Sciences, Genetic and Rare Diseases Information Center. Retrieved from: https://rarediseases.info.nih.gov/diseases/6611/hereditary-amyloidosis.
2-"Hereditary amyloidosis." Amyloidosis Foundation. Retrieved from: http://amyloidosis.org/facts/familial/#attr-amyloidosis.

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The Assistance Fund (TAF) is an independent 501(c)(3) nonprofit organization dedicated to providing financial assistance to patients with serious and chronic diseases. TAF has programs for copay assistance, insurance premiums and incidentals and health care expenses.

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Perfect, we love helping patients.

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I want to

apply for assistance

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see if I'm eligible

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see if my disease is covered

I'm looking for

more information

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Sounds good, we've gathered some topics that may interest you.

What do you want to learn more about?

I want to

see why TAF cares

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see TAF's impact

I want to

know about the process

I want to

read the FAQs

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Great, by working together we can change lives.

What can we do for you?

I want to

partner with TAF

I want to

see TAF's impact

I want to

learn more about TAF

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Excellent, your generosity helps us make a lasting difference.

What would you like to do?

I want to

donate

I want to

see how donations are used

I want to

view TAF's impact

I want to

learn more about TAF

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Take your time.

We compiled a lot of great resources. Here are some topics that we recommend exploring.

I want to

learn why TAF exists

I want to

view TAF's impact

I want to

learn about the process

I want to

learn about TAF

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Great, we'll bring you to the first phase of the application.

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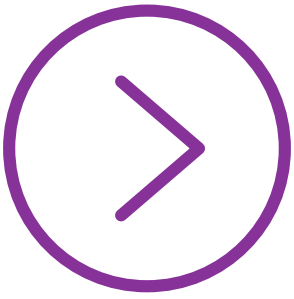

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Our Eligibility page can help you out.

At this page, you can check if you meet the eligibility criteria for our programs.

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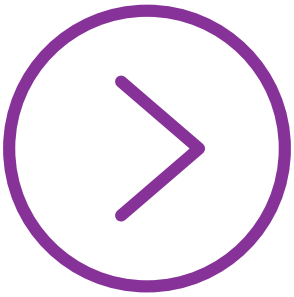

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We have funds for a variety of diseases.

The following page will show you the list of disease states we cover, as well as the programs available for each fund.

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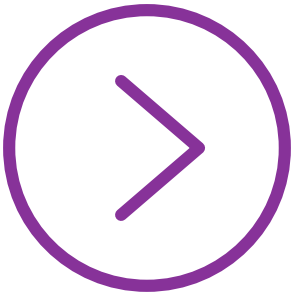

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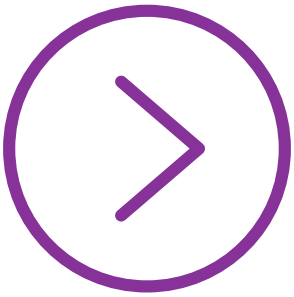

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Visit our impact page and discover the difference we've made over the years.

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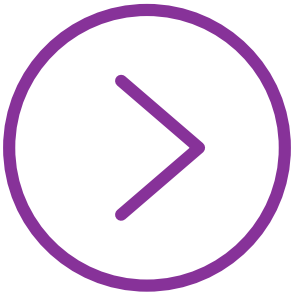

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Find out how the process works.

By clicking below, you'll see what you can expect as a patient after you apply and get approved.

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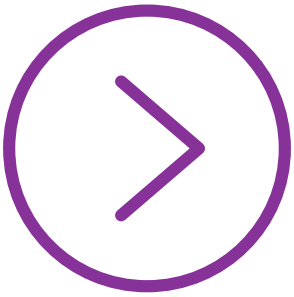

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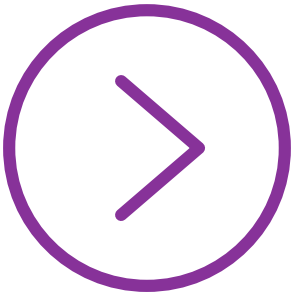

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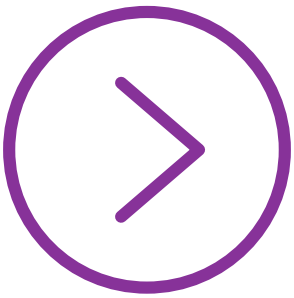

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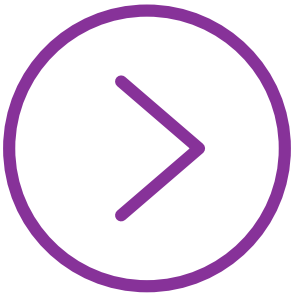

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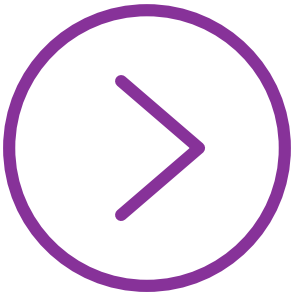

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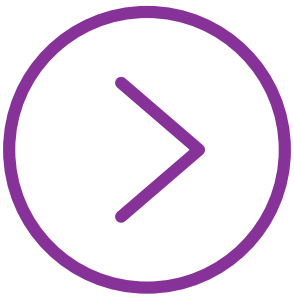

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Learn how funds are allocated by clicking below.

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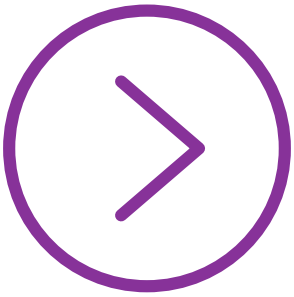

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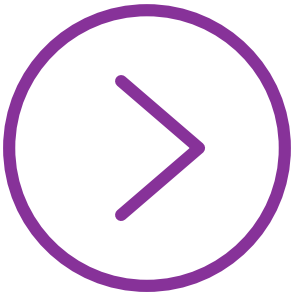

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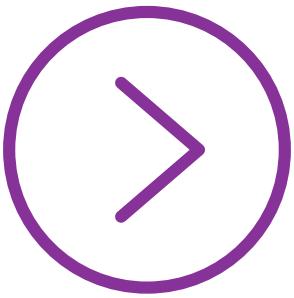

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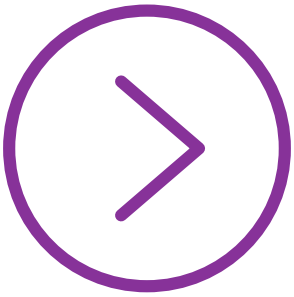

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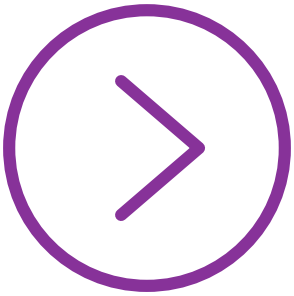

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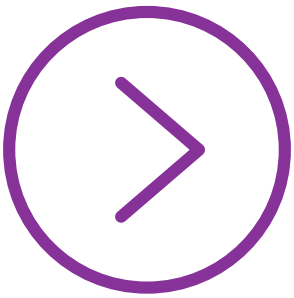

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Learn more about our amazing leadership team as well.

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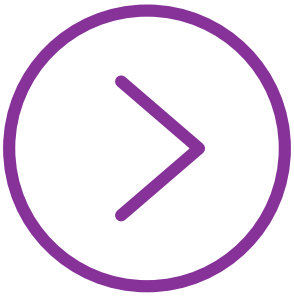

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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

PFIZER INC.

Plaintiff,

v.

UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES,
200 Independence Avenue SW
Washington, DC 20201;

AND

ALEX M. AZAR II, in his official capacity as Secretary of Health and Human Services,
200 Independence Avenue SW
Washington, DC 20201;

AND

UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES OFFICE OF INSPECTOR GENERAL,
330 Independence Avenue SW
Washington, DC 20201;

AND

CHRISTI A. GRIMM, in her official capacity as Principal Deputy Inspector General of and Senior Official in the U.S. Department of Health and Human Services Office of Inspector General,
330 Independence Avenue SW
Washington, DC 20201,

Defendants.

Case: _____

COMPLAINT FOR DECLARATORY JUDGMENT

Plaintiff Pfizer Inc. ("Pfizer") seeks a declaratory judgment against Defendants the United States Department of Health and Human Services ("HHS"), Alex M. Azar II in his capacity as the Secretary of HHS, the HHS Office of Inspector General ("OIG"), and Christi A. Grimm in her

capacity as the Principal Deputy Inspector General of and Senior Official in OIG, and in support thereof, states as follows:

INTRODUCTION

1. Pfizer brings this declaratory judgment action to enable it to provide financial assistance to Medicare beneficiaries who are otherwise unable to afford Vyndaqel® (tafamidis meglumine) or Vyndamax™ (tafamidis) (collectively, "tafamidis" or the "Medications")—two important medical advances and the only pharmacological treatments approved by the U.S. Food and Drug Administration ("FDA") for a rare and fatal heart condition called Transthyretin Amyloid Cardiomyopathy ("ATTR-CM"). Without this Court's intervention, Pfizer is unable to provide this financial assistance because of the significant risk of a criminal or other government enforcement action arising from erroneous legal restrictions imposed by OIG. As a consequence, without relief from this Court, Medicare beneficiaries who are unable to afford copay obligations under the Medicare Part D prescription drug benefit will continue to be denied access to their Medicare benefits and these life-changing medical breakthroughs.

2. The governmental restrictions that are denying patients access to their prescribed medications are a direct result of a series of actions by OIG that, in combination, prevent pharmaceutical manufacturers from providing copay assistance to Medicare Part D beneficiaries, including in the circumstances of Pfizer's proposed programs, on the theory that such assistance constitutes an unlawful kickback. Accordingly, before providing financial assistance to Medicare Part D beneficiaries who cannot afford the out-of-pocket costs of tafamidis, Pfizer is forced to seek a declaratory judgment from this Court that its proposed programs do not violate federal anti-kickback laws.

3. ATTR-CM is a rare medical condition affecting the heart muscle, causing the heart to stiffen and thereby limiting its ability to pump blood to the body. Patients with ATTR-CM experience a progressive decline in function, beginning with fatigue and shortness of breath and ending with potential heart failure, inability to perform even the most basic daily activities, and eventually death. ATTR-CM disproportionately affects individuals over the age of 60 and, in the United States, the hereditary form of the disease primarily afflicts African-American men. No cure exists for ATTR-CM, and, prior to the availability of tafamidis, life expectancy typically was only 2 – 3.5 years from the time of diagnosis. The precise number of people who suffer from ATTR-CM is unknown because the disease historically has been underdiagnosed, but Pfizer estimates the prevalence to be approximately 100,000 – 150,000 patients in the United States based on the best available peer-reviewed literature. FDA confirmed that ATTR-CM is a rare disease under the Orphan Drug Act, a federal statute passed to encourage the development of treatments for such rare conditions.[1]

4. The Medications are the first and only FDA-approved pharmacological treatments for ATTR-CM. Tafamidis was developed after more than a decade of scientific research—including extensive bench testing, animal studies, and clinical trials—and has been shown to significantly reduce mortality, decrease cardiovascular related hospitalizations, and slow the decline in quality of life for people suffering with ATTR-CM. Its approval is a major medical advance that offers real hope to patients suffering with this devastating condition.

[1] Pub. L. No. 97-414, § 1, 96 Stat. 2049 (1983) (codified at 21 U.S.C. § 360bb(a)(2)). The Orphan Drug Act defines a "rare disease or condition" as one "which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug." 21 U.S.C. § 360bb(a)(2).

5. The Medications have a list price of $225,000 for a one-year course of treatment, which is well below comparable novel therapies approved to treat other rare diseases. That price, moreover, is consistent with the Medications' strong efficacy and safety profile, its slowing of the decline in functional status and quality of life, and the relatively small population of patients with ATTR-CM. The Medications also cost substantially less than a dual heart and liver transplant, which is the other potential treatment option for patients with ATTR-CM.

6. Due to the age of the affected population, most ATTR-CM patients are Medicare beneficiaries. Most Medicare plans provide full coverage for tafamidis at the list price, provided prior authorization criteria are met. However, under the standard Medicare Part D benefit structure, a patient must pay significant out-of-pocket costs for tafamidis—approximately $13,000 annually. These costs are prohibitively expensive for many patients. But, because Part D has no cap on beneficiaries' out-of-pocket costs, and because patients are responsible for a coinsurance or percentage of the cost, a reduction in tafamidis' list price—even by half—would not enable many patients to afford the out-of-pocket costs. The result is that tafamidis is only affordable to those patients wealthy enough to pay the out-of-pocket costs or those with incomes so low that Medicare waives most of the out-of-pocket costs under the Low Income Subsidy program. The crux of this action is the legality of Pfizer's efforts to help ATTR-CM patients caught between those financial extremes, who cannot afford to fill their doctor's prescription for the Medications even though they would benefit from these breakthrough treatments.

7. Pfizer is committed to helping ensure that all patients suffering from ATTR-CM can afford these breakthrough Medications. To address that need, Pfizer currently makes the Medications available for free to all ATTR-CM patients—including those on Medicare—who are prescribed the Medications and have annual income up to 500% of the Federal Poverty Level (i.e.,

$86,200 for a family of two in 2020). However, there remain many Medicare patients with incomes above this level who have been prescribed the Medications but are unable to afford the copay and coinsurance requirements of Medicare Part D. Therefore, Pfizer proposes to implement copay assistance programs for middle-income Medicare patients with demonstrated financial need who do not qualify for the other available assistance options. Pfizer already offers a similar program for commercially insured patients, without regard to financial need.

8. These proposed Medicare programs—collectively referred to as "Proposed Copay Assistance Programs" or "Programs"—include (1) directly providing copay and coinsurance assistance to Medicare patients through a copay card or coupon (the "Direct Copay Assistance Program") and (2) funding an existing independent charity that would provide copay assistance to Medicare patients diagnosed with ATTR-CM who require financial support to access tafamidis as well as any other prescription drugs used to treat the symptoms of the disease and any potential side effects of its treatment (the "Independent Charity Program").

9. As detailed below, Pfizer's proposed Programs do not violate federal statutes—specifically the Anti-Kickback Statute, *see* Social Security Act, §§ 1128(b)(7) and 1128A(a)(7), ("AKS") and the Beneficiary Inducement Statute, *see id.* § 1128A(a)(5), ("BIS")—that prohibit kickbacks made with the intent to corrupt medical decision making at the expense of federal health care programs. Rather, the proposed Programs are designed to ensure that financial obstacles do not prevent patients from accessing these breakthrough treatments *after* a physician has objectively determined that a patient has ATTR-CM and prescribed the only FDA approved medications for this terminal disease. Under such circumstances, the Programs do not constitute an illegal kickback.

10. However, as the result of a series of actions by OIG, Pfizer is unable to implement its proposed Programs to assist ATTR-CM patients. Together, these actions establish OIG's position that the AKS and the BIS prohibit pharmaceutical manufacturers (but not others) from providing financial assistance to help Medicare patients cover their out-of-pocket costs, irrespective of the circumstances. OIG has further limited aid to patients by construing the AKS and BIS to impose strict restrictions on pharmaceutical manufacturers' ability to fund and communicate with independent charities that provide financial assistance to Medicare patients. Meanwhile, OIG, in conjunction with the U.S. Department of Justice ("DOJ"), has taken aggressive steps to enforce OIG's strict construction of the AKS and BIS in enforcement actions against pharmaceutical manufacturers who have provided copay assistance or contributed to independent charities that provided financial assistance to Medicare patients. As a result, without a declaration from this Court, Pfizer is prevented from taking action inconsistent with OIG's construction of these statutes.

11. Pfizer supports OIG's mission to enforce the AKS and the BIS to prevent fraud and abuse in the health care system, and nothing in this Complaint should be viewed as an effort to undermine that important goal. But Pfizer disagrees with OIG that the AKS and BIS properly can be construed to prohibit copay assistance when, as in the circumstances of the proposed Programs, the copay assistance does not constitute "remuneration" and is not intended to influence prescriptions for the Medications in the kind of corrupt or improper way addressed by those statutes. For the past year, Pfizer has engaged with OIG through a formal advisory opinion process to obtain OIG's acknowledgement that Pfizer's proposed Programs fall outside the proscriptions of the AKS and BIS, and to obtain OIG's guidance on how the Programs might be modified to address any concerns the agency might have. OIG has refused, however, to acknowledge that

Pfizer's proposed Programs are legal under the AKS and BIS, or to suggest proposed modifications. As a result of OIG's rejection of Pfizer's request and the agency's prior guidance prohibiting pharmaceutical manufacturers from providing copay assistance to Medicare beneficiaries, Pfizer faces significant risks of criminal or other enforcement action if it proceeds with these Programs. Where, as here, Pfizer respectfully disagrees with OIG's conclusion that its proposed Programs would violate those statutes, it is left with no alternative but to seek judicial relief. Pfizer and the very sick patients who will be denied these critical Medications are out of alternatives.

12. In addition, significant First Amendment concerns would be raised if the AKS and BIS were construed, as OIG does, to restrict pharmaceutical manufacturers' communications with and donations to independent charities that provide financial assistance to Medicare patients. OIG's construction burdens Pfizer's established rights to participate in a charitable endeavor and engage in expressive giving in support of patients suffering from ATTR-CM, and improperly singles out pharmaceutical manufacturers for special restrictions on this type of charitable giving. OIG's position, which prohibits certain communications with independent charities concerning financial assistance, is not narrowly tailored to a compelling government interest in combatting fraud or abuse, and therefore violates the First Amendment's Free Speech guarantee.

13. OIG's position on copay assistance leads to perverse and unequal results depending on a Medicare beneficiary's economic status. Under OIG's position, Medicare provides insurance benefits for the Medications for the wealthiest and the poorest Medicare ATTR-CM patients, but effectively denies this same insurance benefit to similarly situated middle-income patients. The wealthiest enrollees can afford tafamidis' out-of-pocket costs; the poorest enrollees will have their out-of-pocket obligations satisfied by Medicare's Low Income Subsidy. For each of these

groups—the wealthiest and the poorest—Medicare pays the remaining share of the Medication's costs. But middle-income Medicare ATTR-CM patients who cannot afford the copay and coinsurance for the Medications forgo filling their prescriptions, and Medicare pays nothing. OIG takes the view that any manufacturer who helps *those* middle-income patients with their out-of-pocket costs has committed health care fraud and may be subject to prosecution or other enforcement action under the AKS and BIS. That interpretation effectively bars middle-income Medicare recipients from accessing their federal health care insurance benefits based solely on their economic status. Such a fundamentally irrational application of the Medicare Part D benefit scheme would violate the equal protection principles enshrined in the Fifth Amendment's Due Process Clause. The AKS and BIS should be interpreted to avoid these constitutional concerns.

14. Accordingly, Pfizer requests a declaration that the Proposed Copay Assistance Programs do not violate the AKS or the BIS.

THE PARTIES

15. Plaintiff Pfizer Inc. is a research-based biopharmaceutical company that develops and manufactures medicines for patients across the globe. Pfizer strives to develop breakthrough therapies that change people's lives, with a focus on internal medicine, inflammation and immunology, oncology, rare diseases, vaccines, sterile injectables, and anti-infectives. Pfizer devotes billions of dollars annually to research in these areas and has developed numerous breakthrough treatments. Pfizer is committed to funding programs that provide public benefit, advance medical care, and improve patient outcomes. To this end, Pfizer collaborates with health care providers, governments, and local communities to support and expand access to reliable, affordable health care. Pfizer is a Delaware corporation with its principal place of business at 235 East 42nd Street, New York, New York 10017.

16. Defendant United States Department of Health and Human Services ("HHS") is an executive department of the United States. HHS oversees multiple health care-related agencies including the Centers for Medicare & Medicaid Services ("CMS"). HHS's headquarters are in Washington, D.C.

17. Defendant United States Department of Health and Human Services Office of Inspector General ("OIG") is an office within HHS that was established in 1976. OIG oversees aspects of the Medicare and Medicaid programs, including through efforts to promote efficiency and economy in departmental operations and to identify and eliminate fraud, abuse, and waste in those programs. The Secretary of HHS has delegated to OIG authority to exclude individuals and entities from participation in federal health care programs, prohibiting payment for any product or service the excluded entity or individual furnishes. The Health Care Fraud and Abuse Control Program, established by the Health Insurance Portability and Accountability Act of 1996 ("HIPAA"), authorizes OIG to provide guidance to the health care industry about potential problems or areas of special interest. OIG's headquarters are in Washington, D.C.

18. Defendant Alex M. Azar II is sued in his official capacity as Secretary of HHS, the most senior official in the department. Under section 1128 of the Social Security Act, as Secretary of HHS, Secretary Azar has direct authority to exclude from participation in federal health care programs any individual or entity convicted of certain offenses or deemed by the Secretary to have engaged in certain improper conduct. Secretary Azar directly supervises the Inspector General and is thus responsible for any guidance that OIG issues as well as OIG's statutory and regulatory enforcement activities.

19. Defendant Christi A. Grimm is sued in her official capacity as Principal Deputy Inspector General of and senior official in OIG. As Principal Deputy Inspector General, Ms.

Grimm is the senior official at OIG and is responsible for its oversight, guidance, rule-making process, and enforcement activities, including its delegated exclusion authority.

JURISDICTION AND VENUE

20. Pfizer brings this action pursuant to the First and Fifth Amendments to the United States Constitution, the Declaratory Judgment Act, 28 U.S.C. §§ 2201-02, and the Administrative Procedure Act, 5 U.S.C. § 702.

21. This Court has jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1361 because Pfizer's causes of action arise under the United States Constitution and laws of the United States.

22. Venue is proper pursuant to 28 U.S.C. § 1391(e) because Pfizer's principal place of business is in this judicial district.

23. There is currently an actual, justiciable controversy between the parties regarding whether Pfizer may, consistent with the AKS and BIS, provide assistance to middle-income Medicare Part D beneficiaries to help them access Pfizer's breakthrough ATTR-CM therapies.

24. Declaratory relief will resolve this controversy and eliminate the chill that the government's interpretation of the statutes and regulations currently has on Pfizer's ability to provide copay assistance.

PFIZER PROPOSES TO PROVIDE FINANCIAL ASSISTANCE TO ALLOW MEDICARE PART D BENEFICIARIES TO ACCESS ITS BREAKTHROUGH THERAPIES FOR A FATAL CARDIAC CONDITION

I. Transthyretin Amyloid Cardiomyopathy ("ATTR-CM") and its Patient Population

25. ATTR-CM is a rare, progressive cardiac condition characterized by deposits of amyloid protein in the heart muscle. Left untreated, a patient with ATTR-CM may suffer progressive heart failure, including severe shortness of breath and limitations on physical activity, which may end in death. In the latter stages of the disease, patients may have difficulty performing even the most basic activities of daily living and frequently require full-time care. Prior to the

availability of tafamidis, patients with ATTR-CM had a median life expectancy of 2 – 3.5 years from diagnosis.

26. Diagnosis of ATTR-CM is made objectively by heart biopsy or nuclear scintigraphy (an imaging technology).

27. The precise number of people who suffer from ATTR-CM is unknown. It is estimated that approximately 100,000 – 150,000 Americans may have the disease, which disproportionately affects the elderly. Most ATTR-CM patients are Medicare beneficiaries and many have limited financial resources.

II. Pfizer's Development of Tafamidis to Treat ATTR-CM

28. Tafamidis is the result of nearly two decades of research and testing. While not a cure, tafamidis offers ATTR-CM patients hope for a longer and better life and may provide a bridge to future therapies.

29. Before development of tafamidis, no FDA-approved pharmacological treatments existed for ATTR-CM. A small number of ATTR-CM patients have undergone dual heart and liver transplants, in hopes of curing the disease, or at least improving their prognosis. These procedures have had some success, but limited application in practice, because most patients with ATTR-CM are too sick and have too many other medical problems to meet transplant criteria. Furthermore, the total cost of an individual patient's transplants can exceed $2 million.

30. The tafamidis molecule first was developed in the early 2000s. Over the next decade, extensive laboratory, pre-clinical, and clinical studies evaluated both the safety and efficacy of the molecule. As with other investigational medicines for rare diseases, these studies were undertaken even though, at the outset, the likelihood of success was very low.

31. Substantial research and development time and costs are required to develop novel therapies like tafamidis. The development of medicines for rare diseases, like ATTR-CM, is

complicated by the fact that the diseases typically are not well characterized or understood, appropriate efficacy endpoints are not defined, and patient populations are very small.

32. These unique challenges make development of medicines for rare diseases even more difficult and expensive. As a consequence of these hurdles, the cost of developing medicines for rare (and other) diseases has continued to rise. As the Office of Health Economics, a British research entity, observed in 2012, biopharmaceutical companies' out-of-pocket drug development expenditures have risen by 600% since the 1970s, while success rates for bringing these developments to market have fallen, making it more expensive than ever for manufacturers to develop rare disease medications.[2]

III. Pfizer's Successful Clinical Trials Demonstrate Tafamidis' Safety and Efficacy in Extending Life for ATTR-CM Patients

33. Pfizer acquired rights to the tafamidis molecule in 2010. In 2012, FDA granted Pfizer orphan drug designation for the development of tafamidis as a treatment for ATTR-CM. Orphan drug designation is a special status FDA may grant to drugs that treat a rare disease, where both the drug and the disease meet certain regulatory and statutory criteria specified in the Orphan Drug Act, 21 U.S.C. § 360bb, and FDA's implementing regulations, 21 CFR Part 316. Orphan designation qualifies the sponsor of the drug for various development incentives designed to encourage innovation of treatments for rare diseases.

34. In 2013, Pfizer began enrollment in the landmark Transthyretin Amyloid Cardiomyopathy Clinical Trial ("ATTR-ACT"), which was an international, multicenter, double-blind, placebo-controlled, randomized clinical trial designed to evaluate the efficacy and safety of tafamidis in patients with hereditary and wild-type ATTR-CM. ATTR-ACT was the largest

[2] Jorge Mestre-Ferrandiz et al., Office of Health Economics, *The R&D Costs of a New Medicine* (Dec. 2012), https://www.ohe.org/publications/rd-cost-new-medicine#.

multicenter investigation of a treatment for ATTR-CM ever conducted, and it was completed after approximately six years in February 2018.

35. The study was sponsored by Pfizer and conducted by leading researchers at some of the most prominent medical institutions in the world, including Columbia University, the Mayo Clinic, Stanford University, the Cleveland Clinic, University College London and St. Bartholomew's Hospital, London, and the French Referral Center for Cardiac Amyloidosis.

36. The study demonstrated tafamidis' value as a breakthrough therapy that changes the lives of patients with ATTR-CM, who until now had no approved medicines for this rare, debilitating, and fatal disease.

37. As reported in the September 13, 2018, issue of the *New England Journal of Medicine,* the combination of all-cause mortality and cardiovascular-related hospitalizations (the primary endpoint of the study) was significantly lower among patients who received tafamidis than among those who received placebo: patients treated with tafamidis had a 30% lower all-cause mortality rate and experienced 32% fewer cardiovascular-related hospitalizations than those taking placebo. At the end of the trial, 70% of tafamidis patients were alive, compared to only 57% of those receiving placebo.

38. More recent data demonstrates tafamidis' immense value to public health. For example, extrapolation of data from the ATTR-ACT study indicates an approximately 18-month increase in median overall survival for patients treated with tafamidis as compared to those receiving placebo.[3]

[3] *See* Benjamin Li *et. al*, *Extrapolation of Survival Benefits in Patients with Transthyretin Amyloid Cardiomyopathy Receiving Tafamidis: Analysis of the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial*. Cardiology and Therapy (Apr. 13, 2020), https://doi.org/10.1007/s40119-020-00179-2; Kumar Dharmarajan and Mathew Maurer, *Transthyretin Cardiac Amyloidoses in Older North Americans*, J. Am. Geriatric Society (Feb. 13, 2012), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3325376/.

39. Tafamidis treatment significantly reduced the decline in patients' functional capacity and quality of life compared to placebo. Given the progressive nature of the disease and the mechanism through which it acts, tafamidis is expected to have greater benefit when administered early in the disease course.

40. Tafamidis was well tolerated in the trial, with a safety profile comparable to placebo and a rate of permanent discontinuation due to adverse events similar to placebo.

41. Based on the results of ATTR-ACT, FDA designated tafamidis a Breakthrough Therapy—a designation reserved for medications "that are intended to treat a serious condition and [for which] preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)."[4]

IV. FDA Approves Tafamidis as the Only Drug to Treat ATTR-CM

42. On May 3, 2019, the FDA approved tafamidis for the treatment of ATTR-CM to reduce cardiovascular mortality and cardiovascular-related hospitalization.

43. Tafamidis is the first and only medicine approved in the United States for treatment of ATTR-CM.

44. The director of the Division of Cardiovascular and Renal Drugs in the FDA's Center for Drug Evaluation and Research described tafamidis as "an important advancement in the treatment of the cardiomyopathy caused by transthyretin-mediated amyloidosis."[5]

[4] *See* FDA, *Breakthrough Therapy*, https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy (last visited June 14, 2020).

[5] FDA, *FDA Approves New Treatments for Heart Disease Caused by a Serious Rare Disease, Transthyretin Mediated Amyloidosis*, (May 6, 2019), https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatments-heart-disease-caused-serious-rare-disease-transthyretin-mediated.

V. The Effect of the Medicare Benefit Design is to Hinder Access to Tafamidis for Middle-Income Americans

45. Medicare is a federal health insurance program that covers individuals age 65 and older, as well those under age 65 with certain disabilities or conditions. Congress enacted Medicare Part D in 2003. 42 U.S.C. § 1395w-101 *et seq.*; Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (2003). Through Part D, Congress made outpatient prescription coverage available to Medicare beneficiaries through private insurance plans, which are approved by Medicare. As of 2019, the Part D program covered 45 million Americans, representing approximately 70% of all Medicare beneficiaries.[6]

46. Congress included a cost-sharing feature in Medicare Part D plans. Under this cost-sharing scheme, the insured patient's out-of-pocket expense for medications is largely driven by the Medicare Part D benefit structure, which has several "phases":

a. ***Deductible.*** Beneficiaries are responsible for a deductible of $435 in 2020, meaning they pay 100% of the first $435 in eligible prescription costs.

b. ***Initial Coverage Phase.*** After beneficiaries have satisfied the deductible, they enter the initial coverage phase, in which they are responsible for a 25% coinsurance payment on any costs up to the initial coverage limit, which in 2020 is $4,020 for combined prescription medication spending by the beneficiary and the Part D plan.

c. ***The "Coverage Gap."*** Once combined prescription medication spending by the beneficiary and plan hits the initial coverage limit ($4,020 in 2020), beneficiaries enter a "coverage gap" phase, often referred to as the "donut hole." In the past,

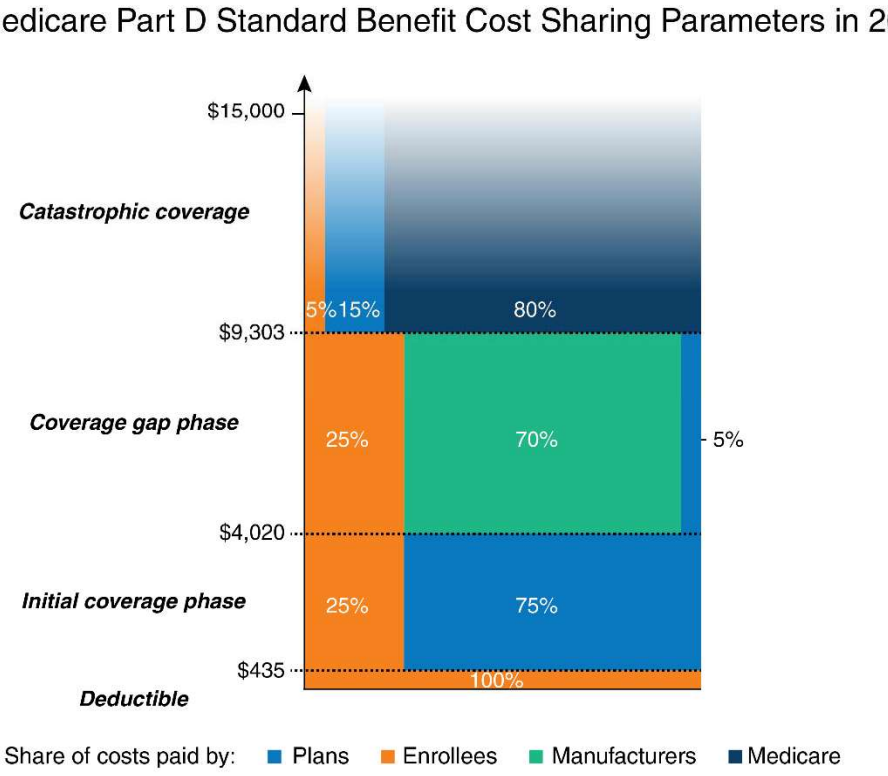
[6] Juliette Cubanski *et al*., *10 Things to Know about Medicare Part D Coverage and Costs in 2019*, Kaiser Family Foundation, (June 4, 2019), https://www.kff.org/medicare/issue-brief/10-things-to-know-about-medicare-part-d-coverage-and-costs-in-2019/.

beneficiaries were responsible for almost all costs when they reached the "donut hole." In more recent years, as a result of changes brought about by the Affordable Care Act, the manufacturer has become responsible for the majority of medication costs during this phase. Still, in 2020, beneficiaries must cover 25% coinsurance payments in this "coverage gap" phase, until they have spent $2,652 out of pocket (inclusive of deductible and initial coverage coinsurance) and reach the catastrophic coverage threshold.[7]

d. ***Catastrophic Coverage.*** Beneficiaries enter the catastrophic coverage phase after their out-of-pocket spending, including during the "coverage gap" phase, reaches $2,652. After beneficiaries reach that threshold, they must continue to pay 5% of the cost of brand-name medications for the remainder of the coverage year. There is no financial cap on the amount that a patient can be required to pay for their medicine in a given year.

47. The below graphic details the standard Part D cost-sharing structure for brand-name medications as of 2020:

[7] This $2,652 figure (nearly 17% increase from 2019) represents the amount that a patient must personally pay out of pocket before reaching the catastrophic coverage threshold if the patient is using only branded medications. If a patient uses a mix of branded and generic medications, the patient's out-of-pocket cost before reaching the catastrophic coverage phase could vary. In addition, to the patient contribution, manufacturers contribute $3,698, for a total co-insurance of $6,350 that the plan does not cover. Juliette Cubanski, and Tricia Neuman, *How Will The Medicare Part D Benefit Change Under Current Law and Leading Proposals?*, Kaiser Family Foundation (Oct. 11, 2019), https://www.kff.org/medicare/issue-brief/how-will-the-medicare-part-d-benefit-change-under-current-law-and-leading-proposals/.



48. Depending on the enrollee's financial situation and the cost of the medicines they may need, Medicare Part D's cost-sharing structure can become financially onerous. In theory, cost sharing is intended to encourage patients to evaluate the need for discretionary care and to consider less expensive alternatives when available. But, in some cases, the Medicare Part D benefit design and patient cost-sharing obligations operate to put even medically necessary treatment out of reach for patients.

49. Congress made clear that it did not intend cost sharing to operate as a mechanism to ration access to essential medications (or to limit Part D benefits to only those wealthy enough to afford copay or coinsurance amounts). To mitigate against that result, Congress included in Medicare a Low Income Subsidy ("LIS") program that limits the impact of the Medicare Part D cost-sharing structure by providing additional coverage to patients falling below 150% of the Federal Poverty Level. To qualify for Medicare's LIS program, patients must earn less than

$19,140 annually. As a result of this income threshold, LIS assistance is unavailable to the majority of Medicare beneficiaries: of the approximately 45 million Part D enrollees in 2016, only an estimated 13 million (29%) qualified for the LIS program.[8]

50. Some patients for whom LIS is unavailable may obtain financial assistance through charities or from manufacturer-supported free drug programs, such as Pfizer's free drug program for tafamidis. If neither charitable assistance nor free medication is available, then a patient who is not wealthy but does not qualify for the LIS program may be forced to forgo treatment. Even where charitable assistance is obtained initially, a patient is not assured that it will continue to be available to help the patient with copays on a long-term basis.

51. Indeed, there is evidence that at least one quarter of new Medicare Part D prescriptions are abandoned if patients are asked to pay $50 or more (which is why Pfizer proposes a copay of $35 in its Proposed Programs).[9] The problem becomes more acute for beneficiaries with cancer or rare diseases, where the cost of developing treatments and a smaller patient population results in the manufacturer charging higher prices. Despite the severity of these diseases, the higher out-of-pocket costs of these medications cause many prescriptions to go unfilled and patients to go without treatment. In one study, 49% of cancer patients who had out-of-pocket costs over $2,000 did not fill their prescriptions. By comparison, the rate of unfilled prescriptions was only 10% amongst patients paying less than $10 for their prescriptions.[10]

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[8] Jack Hoadley et al., *Medicare Part D in 2016 and Trends over Time*, Kaiser Family Foundation, (Sept. 16, 2016), https://www.kff.org/report-section/medicare-part-d-in-2016-and-trends-over-time-section-4-the-low-income-subsidy-program/.

[9] *Drug pricing in America: A prescription for Change, Part II, Hearing Before the Senate Comm. on Finance*, 116th Cong 66 (2019) (prepared statement of Albert Bourla, DVM, Ph.D., Chief Executive Officer, Pfizer). https://www.finance.senate.gov/imo/media/doc/37143.pdf.

[10] Jalpa A. Doshi, et al., *Association of Patient Out-of-Pocket Costs with Prescription Abandonment and Delay in Fills of Novel Oral Anticancer Agents,* J. of Clinical Oncology 476, (Feb. 10, 2018), https://ascopubs.org/doi/full/10.1200/JCO.2017.74.5091.

52. Tafamidis exemplifies the challenges to patient affordability resulting from Medicare's benefit design when it is applied to medicines that treat a rare disease and are, consequently, more expensive. Under the Medicare Part D benefit structure, a patient must pay approximately $13,000 in annual out-of-pocket expenditures for tafamidis, based on mandatory coinsurance through certain Part D phases (*i.e.,* deductible, initial benefit limit, coverage gap, and catastrophic) and certain formulary tiers (*e.g.,* specialty tier). This expense presents a prohibitive financial barrier for a significant proportion of Medicare patients.

53. Reduction in drug prices will not solve the affordability problem for innovative orphan drugs like tafamidis under Medicare Part D's benefit structure. That is because Medicare Part D front loads costs by requiring patients to pay at least $2,652 of their medicines' costs before they reach the catastrophic coverage phase of the benefit—an onerous threshold that prevents access to most innovative orphan drug treatments. Moreover, after a beneficiary hits the catastrophic coverage phase, Part D's lack of an out-of-pocket spending cap means patients are still responsible for significant co-insurance costs. Thus, even if tafamidis' price were cut in half, the $2,652 initial out-of-pocket costs to patients would not be reduced at all and the total cost to patients, approximately $8,000 annually, would remain prohibitive for most patients.

54. For many Part D enrollees, spending thousands of dollars in annual prescription expenses is beyond their means. Those patients will not be able to fill their prescription and, without assistance, will be forced to forgo the treatment.

55. The result is that, without assistance, many ATTR-CM patients will not be able to afford the Medications that can help extend their lives.

56. The Medicare Part D statute or regulations do not directly prohibit manufacturers or other entities from providing copay assistance to Medicare patients.

57. As discussed below, however, OIG has construed the AKS and BIS to categorically ban manufacturers, but not others, from offering copay assistance to Medicare patients under any circumstances. OIG's interpretation of those statutes also substantially restricts manufacturer support of independent charities that could provide such financial support. That construction improperly expands the prohibitions in the AKS and BIS, which are aimed at preventing fraud and bribery in medical decision-making. In so doing, OIG's position broadly blocks patients' access to Medicare coverage in a manner not contemplated by Congress when it established the Part D program.

VI. Pfizer's Proposed Copay Assistance Programs Would Allow Medicare Patients to Access these Breakthrough, Life-Extending Medications

58. Pfizer's Proposed Copay Assistance Programs would help ensure that financial obstacles do not prevent ATTR-CM patients, who have been appropriately prescribed tafamidis, from receiving the medication. More specifically, Pfizer proposes two possible solutions to facilitate patient access. Pfizer seeks to provide financial assistance to such patients to help them cover out-of-pocket expenses (copay and coinsurance) through the Direct Copay Assistance Program and/or the Independent Charity Program, which would mean funding an existing independent charity that would provide copay assistance to patients diagnosed with ATTR-CM who require financial support to access tafamidis (the only FDA-approved treatment for the disease state) as well as any other ancillary prescription drugs used to treat the symptoms of the disease and any potential side effects of treatment. Collectively, these are described as the "Proposed Copay Assistance Programs."

59. If Pfizer were to implement the Proposed Copay Assistance Programs, the out-of-pocket cost for eligible patients with Medicare insurance would be $35 per month for tafamidis.

60. The following paragraphs outline the proposed Programs that Pfizer has designed to help middle-income Medicare patients access the Medications. As discussed below, Pfizer submitted to OIG a request for an advisory opinion on the permissibility of the Proposed Copay Assistance Programs, as characterized herein. OIG refused to issue an advisory opinion on the Independent Charity Program and has informed Pfizer that it has reached an unfavorable opinion on the Direct Copay Assistance Program. At this juncture, Pfizer cannot proceed with either of the Proposed Copay Assistance Programs without facing a significant and imminent risk of enforcement action.

A. Direct Copay Assistance Program

61. The proposed Direct Copay Assistance Program would provide copay assistance directly to eligible Medicare Part D beneficiaries to help them pay the costs required to matriculate through the Part D deductible, initial coverage phase, and coverage gap and then to assist patients with affording the 5% coinsurance required during the catastrophic phase.

62. To be eligible to receive copay assistance under this Program, patients must: (1) be prescribed tafamidis for an on-label (approved) indication, that is, ATTR-CM; (2) be United States residents; and (3) meet program criteria for financial need tailored to address the burden otherwise faced by middle-income patients who are unable to access other available resources. Part D beneficiaries meeting those requirements who enroll in the program would pay a copay of $35 per month, after which Pfizer would pay 100% of each enrolled Medicare Part D beneficiary's monthly deductible or coinsurance amounts for tafamidis.

63. Pfizer would not advertise its Direct Copay Assistance Program or use it as a means to solicit new patients for tafamidis. Rather, the Direct Copay Assistance Program would offer copay assistance only after a physician diagnoses a patient with ATTR-CM and decides to prescribe tafamidis.

64. Nor would Pfizer routinely provide copay assistance to all patients prescribed tafamidis. Rather, patients requesting assistance through the Direct Copay Assistance Program would be individually evaluated, on a case-by-case income determination, based on a uniform measure of financial need, to ensure that patients meet the Program requirements. Pfizer would require patients to provide appropriate documentation to substantiate those financial need determinations.

65. The Direct Copay Assistance Program provides no financial incentive to physicians to favor tafamidis. Prescribers would exercise independent medical judgment on whether a patient should use tafamidis based on its efficacy and safety for treating ATTR-CM, after objective diagnosis of that condition and based on each patient's medical profile and treatment needs. Prescribers would receive no benefit from the program. Indeed, physicians currently prescribe tafamidis to ATTR-CM patients covered by Medicare in the absence of any direct copay assistance program, and they do so because tafamidis is the only approved medication for this deadly disease and because of its proven clinical benefits.

66. The Direct Copay Assistance Program has no more impact on a physician's prescribing decision for impacted patients than does the existence of the LIS program for indigent patients or the availability of existing financial assistance programs from Pfizer or any other third-party source.

67. The Direct Copay Assistance Program would put middle-income Medicare patients demonstrating financial need on similar footing as commercially insured patients suffering from ATTR-CM, who already benefit from Pfizer's copay assistance. The only difference between these patients is the type of insurance to which they have access.

68. Because no alternative pharmacologic therapies have been approved to treat ATTR-CM (and a dual organ transplant is both far more expensive and rarely a viable option), the proposed arrangement presents no risk of inappropriately steering ATTR-CM patients toward tafamidis or improperly inducing prescriptions for tafamidis.

69. In summary, the Direct Copay Assistance Program will enable patients to access the sole effective treatment for ATTR-CM and put middle-income patients on similar footing with wealthy patients who can afford the out-of-pocket costs, low-income patients who qualify for LIS subsidies, and commercially insured patients who have access to Pfizer's analogous patient assistance programs. The Program will advance Medicare's purpose and improve patient care, and does not constitute an illegal kickback, as discussed below.

B. Independent Charity Program

70. Pfizer's proposed Independent Charity Program would fund an existing independent charity to develop a copay assistance fund specifically for ATTR-CM patients.

71. The independent charity would provide copay assistance to patients diagnosed with ATTR-CM who require financial support to access tafamidis and any other prescription drugs used to treat the symptoms of the disease and any potential side effects of treatment. These other prescription drugs would include other manufacturers' products, and they would be ancillary to the treatment of the disease state itself.

72. Pfizer would communicate with the charity about the scope of the fund and funding needs, but the charity would retain independence to establish patient eligibility criteria, to ensure patients make a showing of financial need and have been appropriately prescribed tafamidis, and to determine how to allocate funds.

PFIZER'S PROPOSED COPAY ASSISTANCE PROGRAMS ARE LAWFUL AS A MATTER OF PROPER STATUTORY CONSTRUCTION

I. The Anti-Kickback Statute ("AKS") and Beneficiary Inducement Statute ("BIS")

A. The Anti-Kickback Statute ("AKS")

73. The AKS is a criminal statute originally enacted as part of the Social Security Amendments Act of 1972 to combat fraud and abuse in the Medicare and Medicaid programs.

74. The AKS prohibits any person from knowingly and willfully offering, paying, soliciting, or receiving "remuneration" (*i.e.*, a thing of value), directly or indirectly, in cash or in kind, "to induce" the purchase, prescription, or recommendation of items or services payable under a federal health care program. 42 U.S.C. § 1320a-7b(b)(2).

75. Conviction under the AKS can result in severe consequences for pharmaceutical manufacturers, executives and employees, including the imposition of criminal or civil penalties (including serving as the basis for liability under the False Claims Act), and/or administrative sanctions. *See* 42 U.S.C. § 1320a-7(b)(15). Most dire for a pharmaceutical company, conviction can serve as grounds to exclude the company and its products from reimbursement under federal health care programs, including Medicare and Medicaid. 42 U.S.C. § 1320-7(a) and (b). Due to the outsized role of federal health insurance in the health care sector, a pharmaceutical company cannot afford the risk of exclusion.

76. Because the literal language of the AKS could be read very broadly and the consequences of conviction are so severe, Congress has enacted various statutory exemptions for different types of conduct that it would not want to deter. 42 U.S.C. § 1320a-7b(b)(3). The statutory exceptions demonstrate that Congress intends for the AKS to apply only in circumstances where the remuneration is intended to improperly or corruptly influence the relevant individual's decision-making.

77. In addition, Congress ordered HHS to promulgate regulatory "safe harbors," which define certain types of payments and other arrangements that cannot be the basis for criminal or civil liability even if they arguably might violate the literal language of the AKS if read broadly.[11] 42 U.S.C. § 1320a-7b(b)(3)(E). OIG has adopted 28 safe harbors that are currently in effect.

B. The Benefit Inducement Statute ("BIS")

78. The BIS, enacted as part of HIPAA in 1996, prohibits any person, organization, or entity from "offer[ing] to or transfer[ing] remuneration to any individual eligible for [Medicare, Medicaid or certain other federally funded State health care programs] . . . that such person knows or should know is likely to influence such individual to order or receive from a particular provider, practitioner, or supplier any item or service for which payment may be made, in whole or in part," under federal health care programs. 42 U.S.C. § 1320a-7a(a)(5). The BIS also carries significant civil monetary penalties. *Id.* § 1320a-7a(a).

C. The "Remuneration" Element

79. Not all monetary payments qualify as "remuneration" under the BIS or under the AKS's implementing regulations. Even though "remuneration" can include "anything of value," the BIS statute and AKS regulations create an exception for copay waivers (the "Copay Waiver Exception"). Under the BIS, waivers of coinsurance or deductibles are not "remuneration" if: (i) the waiver is not offered as part of any advertisement or solicitation; (ii) the person does not routinely waive coinsurance or deductible amounts; and (iii) the person waives the coinsurance

[11] The Senate Committee Report explained Congress' intent in creating regulatory "safe harbors" as follows: "It is the understanding of the Committee that the breadth of [the] statutory language has created uncertainty among health care providers as to which commercial arrangements are legitimate, and which are proscribed. The Committee bill therefore directs the Secretary, in consultation with the Attorney General, to promulgate regulations specifying payment practices that will not be subject to criminal prosecution ... and that will not provide a basis for exclusion from participation in Medicare or the State health care programs." S. Rep. No. 109, 100th Cong., 1st Sess. 14 (1987), reprinted in 1987 U.S.C.C.A.N. News 682, 707.

and deductible amounts after determining in good faith that the individual is in financial need or fails to collect coinsurance or deductible amounts after making reasonable collection efforts. 42 U.S.C. § 1320a-7a(i)(6)(A). The regulations implementing the AKS create a similar Copay Waiver Exception to the definition of "remuneration." 42 C.F.R. § 1003.110.

80. In addition, the BIS creates an Access to Care Exception, which excludes from the statutory definition of "remuneration" arrangements that "promote[] access to care" and pose a low risk of harm to patients and federal health care programs. 42 U.S.C. § 1320a–7a(6)(D); 81 Fed. Reg. 88,368, 88,393 (Dec. 7, 2016) (regulations implementing Access to Care Exception).

81. According to OIG's regulations, an arrangement will pose a low risk of harm under the Access to Care Exception if it is "(1) . . . unlikely to interfere with, or skew, clinical decision making; (2) … unlikely to increase costs to federal health care programs or beneficiaries through overutilization or inappropriate utilization; and (3) [does] not raise patient safety or quality-of-care concerns." 81 Fed. Reg. 88,368, 88,396 (Dec. 7, 2016); 42 C.F.R. § 1003.110 (2017).

82. Through these regulations, OIG has acknowledged that not all programs that eliminate financial obstacles that might prevent a patient from filling a prescription present a risk of over or inappropriate utilization.

83. OIG has, however, prevented individuals or companies from independently taking advantage of the statutory exception, by requiring them first to satisfy OIG that the exception is warranted. By regulation, OIG places the burden on "anyone asserting this exception . . . of presenting sufficient facts and analysis" to prove to OIG in advance that the particular arrangement promotes access to care and poses no more than a low risk of harm to patients or federal health care programs. 81 Fed. Reg. 88,368, 88,391 (Dec. 7, 2016).

D. **The "Inducement" Element**

84. A payment only violates the AKS or BIS if it is provided "knowingly and willfully . . . *to induce*" the purchase, prescription, or recommendation of items or services payable under a federal health care program.

85. In order to satisfy the inducement element of the AKS and BIS, the government must show that the defendant paid remuneration in an "attempt to gain influence over the reason or judgment of that person," where "that person" refers to the individual who received remuneration under the preceding inquiry. *United States v. Krikheli*, 461 F. App'x 7, 10–11 (2d Cir. 2012).

86. The requisite influence must be "improper," *see, e.g.*, *United States v. TEVA Pharm. USA, Inc.*, No. 13 CIV. 3702 (CM), 2016 WL 750720, at *17 (S.D.N.Y. Feb. 22, 2016); *Guilfoile v. Shields*, 913 F.3d 178, 192–93 (1st Cir. 2019), and the accompanying remuneration must be "offered or paid as a *quid pro quo*," *Krikheli*, 461 F. App'x at 10–11. "[T]he government [i]s required to prove that any payments . . . were made to induce referrals in a *quid pro quo* transaction." *Id.*

87. This requirement that the influence be "improper" or "corrupt," *i.e.*, in the nature of a "*quid pro quo*," is consistent with the Supreme Court's recognition that "kickback" has an established, circumscribed meaning under federal statutes, such as 41 U.S.C. § 8701(2), which defines "kickback" as a thing of value given "*for the purpose of improperly obtaining* or rewarding favorable treatment." *Skilling v. United States*, 561 U.S. 358, 412-13 (2010) (emphasis added) (citing also 18 U.S.C. § 666(a)(2) ("*corruptly* gives … anything of value … with intent to influence or reward"), and 18 U.S.C. § 201(b) (same)).

II. The Proposed Copay Assistance Programs Do Not Violate the AKS or BIS

88. Pharmaceutical manufacturer copays to federal health insurance beneficiaries are lawful under the AKS and BIS when, as in the case of tafamidis, the manufacturer does not knowingly and willfully intend for those copays to improperly or corruptly influence the prescribing or purchase of its product. Here, the proposed Programs do not meet either the remuneration or inducement elements of the AKS and BIS.

A. The Proposed Copay Assistance Programs Do Not Involve Prohibited Remuneration

i. The Copay Waivers Here Are Specifically Exempted from the Definition of "Remuneration"

89. The financial assistance to be provided under the Proposed Copay Assistance Programs meets each of the three requirements for the Copay Waiver Exception to the BIS and AKS implementing regulations. 42 U.S.C. § 1320a-7a(i)(6)(A) (BIS); 42 C.F.R. § 1003.110 (AKS implementing regulations). It would not be offered as part of any advertisement to solicit prescriptions for tafamidis; rather, it would be offered only to patients diagnosed with ATTR-CM who have already been prescribed tafamidis by their physician. Moreover, the waivers would not be "routine," as they instead would be granted on a case-by-case basis upon a documented demonstration of financial need based on objective criteria.

90. Additionally, the proposed Programs meet the Access-to-Care Exception because they increase access to necessary medical care and pose a low risk of harm to federal health care programs. 42 C.F.R. § 1003.110 (definition of "remuneration"); 81 Fed. Reg. 88,368, 88,393 (Dec. 7, 2016):

a. *The Proposed Copay Assistance Programs Do Not Interfere with Clinical Decision-Making*. Tafamidis is an FDA-designated "breakthrough therapy," the only FDA-approved medication for treatment of ATTR-CM, and the only treatment proven to reduce

mortality and slow decline in function and quality of life for patients with this deadly disease. As noted above, there are no realistic alternative treatments for the overwhelming majority of Medicare patients suffering from ATTR-CM and any copay assistance would be available only *after* the objective diagnostic and prescribing decisions of the patient's treating physician. Under those circumstances, copay assistance would not improperly alter clinical decision-making.

b. *The Programs Promote Appropriate Utilization, Not Overutilization*. As discussed above, only patients diagnosed with ATTR-CM who are prescribed tafamidis on-label by their physician and who have demonstrated financial need will be eligible for copay assistance. Thus, the effect of the Proposed Copay Assistance Programs would not be to induce unwarranted prescriptions, but to help ensure that appropriate patients have access to therapy regardless of their ability to pay. The lack of alternatives to tafamidis also eliminates the concern that patients could be locked into a particular product because of financial incentives. Any additional expenditure required for tafamidis would be appropriate and necessary to allow patients suffering from a debilitating and fatal condition to benefit from a breakthrough treatment that can extend life, as evidenced by Medicare's willingness to pay its share of tafamidis' cost for patients covered by LIS or beneficiaries who are able to afford their coinsurance obligations from their personal resources or other third-party sources.

c. *The Programs Promote Patient Safety and Quality of Care*. For most patients with ATTR-CM, tafamidis will be the best and only available treatment. The fact that the Programs would increase access to tafamidis for appropriate patients would improve the quality of patient care and patient outcomes. Copay support in this context—whether from an independent charity or directly from Pfizer—is designed to allow doctors to make treatment decisions based on their

patients' best clinical interest, ensuring that financial need does not impede patient access to these life-changing Medications.

ii. The Proposed Independent Charity Program, by Involving an Independent Charitable Organization, Takes the Assistance Even Further from Remuneration

91. The proposed Independent Charity Program is even further outside the statutory prohibitions of the AKS and BIS, because the ostensible remuneration would not be provided ***to*** the person who would supposedly be induced.

92. The AKS and the BIS only encompass transfers of remuneration to a person in order to corruptly induce or influence ***that person's*** decisions about the provision of medical services funded under a federal health care program. *See* 42 U.S.C. § 1320a-7b(b)(2)(B); 42 U.S.C. § 1320a-7a(a)(5). While the connection between the remuneration and the induced individual can be "direct[] or indirect[]," 42 U.S.C. § 1320a-7b(b), there still must be a causal chain connecting the two.

93. As OIG has long acknowledged in its guidance, making charitable donations to an independent organization that facilitates access to medication does not qualify as prohibited remuneration provided—even indirectly—"to" the person to be induced as long as the charity remains independent and the donations are not intended to improperly induce the independent organization to recommend or arrange for the purchase of the manufacturer donor's federally reimbursable items. Precisely because the "bona fide charitable assistance programs" are "independent," the manufacturers that contribute to the independent charity are not providing prohibited "remuneration" to any specific patient.

94. Nor does the fact that tafamidis is the only FDA-approved treatment option for ATTR-CM change the analysis under the AKS' and BIS' remuneration prong, which hinges on the bona fide independence of the charity, not the breadth of its charitable goals. Through guidance

issued in both 2005 (the "2005 Guidance") and 2014 (the "2014 Guidance"), OIG has acknowledged the fact that "a disease fund includes only one drug or drugs made by one manufacturer would not, standing alone, be determinative of an anti-kickback statute violation." 70 Fed. Reg. 70,623-03, 70,627 n.19 (Nov. 22, 2005); 79 Fed. Reg. 31,120, 31,122 (May 30, 2014). Once again, the independence of the charity means that the manufacturer has not provided "remuneration" to the patient, even when a charitable fund, by its own design, supports only one approved product.

95. OIG's 2005 Guidance suggests that certain communications with independent charities can undermine their independence and turn them into a "conduit" for manufacturers to provide copay support to patients. 70 Fed. Reg. 70,623, 70,626-27 (Nov. 22, 2005). However, merely communicating with a charity about the levels of funding or other means of making the donation more effective does not eliminate that independence and transform those donations into remuneration.

B. The Proposed Copay Assistance Programs Are Not Intended to Improperly Induce Prescriptions for Tafamidis

96. In the circumstances of the Proposed Copay Assistance Programs, patient assistance would not "improperly" or "corruptly" influence the "reason or judgment" of a patient to fill a prescription for tafamidis.

97. Under the Proposed Copay Assistance Programs, any offer of copay assistance will occur only ***after*** a physician has diagnosed a patient with ATTR-CM on the basis of objective criteria and prescribed tafamidis. Moreover, the fatal nature of the disease, and the absence of alternative therapies, obviates concerns for over- or inappropriate utilization. In these circumstances, the Proposed Copay Assistance Programs will facilitate access to tafamidis, remove

barriers to therapy, and encourage adherence to science-based treatment decisions. The Programs will not improperly induce or influence either the physician's or patient's decision-making.

98. Patients who are diagnosed with ATTR-CM have only three options: (1) they can live with a progressive, debilitating disease that results in death, typically within 2 to 3.5 years; (2) they can see if they are medically eligible for a more expensive, more invasive, and more dangerous dual heart and liver transplant; or (3) they can take a prescribed course of tafamidis. Faced with those choices, the notion that the Proposed Copay Assistance Programs induce—much less *improperly* induce—a patient to choose the third option is unsupportable.

IN LIGHT OF OIG'S INTERPRETATION OF ANTI-FRAUD STATUTES, PFIZER CANNOT IMPLEMENT THE PROPOSED PROGRAMS WITHOUT SIGNIFICANT RISK OF INCURRING AN ENFORCEMENT ACTION

99. Notwithstanding the clear social and medical benefits of Pfizer's Proposed Copay Assistance Programs, which would allow middle-income Part D beneficiaries to access tafamidis in the same way their wealthier and poorer fellow Medicare beneficiaries do, OIG's overly broad interpretation of the AKS and BIS prevents Pfizer from doing so. OIG's interpretation is wrong, and Pfizer's Proposed Copay Assistance Programs are lawful as a matter of proper statutory construction.

100. Congress enacted the AKS and BIS to combat health care fraud. OIG, however, has adopted the view that the AKS and the BIS categorically prohibit pharmaceutical manufacturers from providing direct copay assistance to Medicare patients (and other federal health care beneficiaries), irrespective of whether such assistance would provide access to critically needed medications, rather than improperly corrupt medical decision-making. This view is clear from OIG's guidance documents and enforcement history regarding pharmaceutical copay assistance to Medicare patients, and from OIG's rejection of Pfizer's request for an advisory

opinion supporting the Programs. OIG has further issued guidance that imposes severe limitations on pharmaceutical manufacturers' funding of, and communications with, independent charities that provide financial assistance to Medicare patients. The combination of OIG's actions effectively prevents Pfizer from implementing its proposed Programs, even though they do not violate federal kickback laws.

I. OIG's Rejection of Pfizer's Request for an Advisory Opinion Supporting Direct Copay Assistance for Tafamidis

101. Because many entities could reasonably fear that their common, lawful business activities might arguably fall within the literal language of the AKS and BIS, even though they raise no genuine concern of fraud, Congress enacted a process by which an entity could seek an advisory opinion that its proposed conduct would not violate the statute. 42 U.S.C. § 1320a-7d(b). The entity could also seek an advisory opinion that the proposed activity does not "constitute[] grounds for the imposition of a sanction" of exclusion. 42 U.S.C. § 1320a-7d(b)(2)(E). Congress went so far as to provide that the OIG's opinion would be binding on both OIG and the requestor. 42 U.S.C. § 1320a-7d(b)(4)(A).

102. This highly unusual statutory procedure reflects Congress's desire not to chill socially beneficial behavior.

103. On June 27, 2019, Pfizer submitted to OIG a request for an advisory opinion on the legality of both the Independent Charity Program and the Direct Copay Assistance Program.

104. On August 2, 2019, OIG rejected that request, indicating that it was "not able to issue an advisory opinion" as to the Independent Charity Program "because 'the same or substantially the same course of action is under investigation, or has been the subject of a[n]

[enforcement] proceeding involving [HHS] or another governmental agency.'"[12] On August 26, 2019, after conferring with OIG, Pfizer resubmitted this request, limiting it to the Direct Copay Assistance Program and excluding the Independent Charity Program.

105. On December 9, 2019, OIG orally informed Pfizer that it had reached an unfavorable opinion on the Direct Copay Assistance Program because the Program would implicate the AKS and BIS, and that OIG would issue an opinion to that effect if Pfizer did not voluntarily withdraw the request.[13]

106. In response to OIG's December 9, 2019 decision, Pfizer sought a further meeting with OIG to explain why Pfizer believed its Direct Copay Assistance Program did not violate the AKS or BIS, and, furthermore, why there was little risk of fraud or abuse given the particular characteristics of tafamidis as the sole FDA-approved medication to treat ATTR-CM.

107. During a teleconference with OIG on March 30, 2020, and in a follow-up written letter, Pfizer further clarified the steps it would take to ensure that the Direct Copay Assistance Program would be limited to eligible beneficiaries of federal health care insurance who had been objectively diagnosed with ATTR-CM, had been prescribed tafamidis by their physician, and were only unable to access their medication due to financial need.

108. Nonetheless, on May 26, 2020, OIG informed Pfizer that its position was unchanged and it would issue an unfavorable advisory opinion on the Direct Copay Assistance Program if Pfizer did not voluntarily withdraw the request. OIG declined to provide Pfizer any

[12] Based on discussions with OIG, it is Pfizer's understanding that the conduct under investigation was not Pfizer's donations to independent charities but the conduct of other companies.

[13] This is OIG's common practice when it has reached an unfavorable decision on a request for advisory opinion. *See* HHS OIG, *Advisory Opinion FAQs* (stating that OIG "generally find[s] that informal consultation with the requesting parties helps us with our review and analysis of requests" and that it "will initiate discussions with a requesting party's designated contact person at the point at which we would find such discussions useful," but also noting that "regulations permit the requesting party to withdraw its request at any time before the opinion is issued"), https://oig.hhs.gov/faqs/advisory-opinions-faq.asp (last visited June 25, 2020).

feedback regarding how the Direct Copay Program could be modified such that OIG would give a favorable opinion. Pfizer accordingly has no further administrative avenues of relief to pursue with OIG.

109. OIG's long-standing guidance, and its decision to reject Pfizer's request for a supportive advisory opinion on the proposed Programs, leave Pfizer unable to engage in its desired conduct and with no avenues for further agency review. Absent this Court's intervention, Pfizer's only options are to comply with OIG's current interpretation of the AKS and BIS in its guidance, or else, go forward subject to the significant and credible threat of enforcement. If the Court declares, however, that the proposed Programs do not constitute prohibited "remuneration" or result in any improper "inducement," and thus do not violate either the AKS or BIS, then Pfizer would be free to initiate the Programs.

II. OIG Guidance Improperly Restricts Copay Assistance and Interactions with Independent Charity Programs that Benefit Medicare Patients

110. OIG has issued a series of guidance documents that establish its position that direct copay assistance is prohibited by the AKS and BIS and establishing severe restrictions on pharmaceutical manufacturers' ability to fund and interact with independent charities that provide financial support to federal health care beneficiaries. [14]

A. OIG's Limits on Direct Copay Assistance to Federal Health-Care Beneficiaries

111. In its 2005 Guidance, OIG stated its position that cost-sharing subsidies provided by "pharmaceutical manufacturer" patient assistance programs to Medicare Part D patients to help with out-of-pocket costs "would implicate the anti-kickback statute and pose a substantial risk of program and patient fraud and abuse" under Medicare Part D. 70 Fed. Reg. 70,623-03, at 70,625

[14] The Health Care Fraud and Abuse Control Program, established by HIPAA, authorizes OIG to provide guidance to prevent fraud and abuse. As part of this mandate, OIG issues Special Advisory Bulletins about industry practices or arrangements that potentially implicate the fraud and abuse authorities subject to enforcement by OIG.

(Nov. 22, 2005). Even more categorically, OIG stated that manufacturer "subsidies [for their Part D drugs] would be squarely prohibited by the statute, because the manufacturer would be giving something of value (*i.e.*, the subsidy) to beneficiaries to use its product." *Id.*

112. OIG has further stated its view that manufacturer copay assistance programs "present all of the usual risks of fraud and abuse associated with kickbacks, including steering beneficiaries to particular drugs; increasing costs to Medicare; providing a financial advantage over competing drugs; and reducing beneficiaries' incentives to locate and use less expensive, equally effective drugs." *Id.* On those bases, OIG concluded that such programs could cause "[i]ncreased costs to the [Medicare] program" by inducing overutilization and could cause "[b]eneficiary steering and anti-competitive effects" by "locking beneficiaries into the manufacturer's product, even if there are other equally effective, less costly alternatives (and even if the patient's physician would otherwise prescribe one of these alternatives)." *Id.* at 70,625-26.

113. OIG's 2014 "Special Advisory Bulletin"[15] further advised pharmaceutical manufacturers that "copayment coupons" that "reduce or eliminate the cost of [patients'] out-of-pocket copayments . . . constitute remuneration offered to consumers to induce the purchase of specific items" and therefore, OIG found they implicate the AKS. OIG warned that, "[p]harmaceutical manufacturers that offer copay coupons may be subject to sanctions" if they fail to ensure that the coupons are not used by Part D beneficiaries.[16] That warning was categorical without any indication that OIG would *ever* view copay coupons as permissible for federally

[15] HHS OIG, Special Advisory Bulletin – Pharmaceutical Manufacturer Copayment Coupons, (Sept. 2014), https://oig.hhs.gov/fraud/docs/alertsandbulletins/2014/SAB_Copayment_Coupons.pdf. The Health Care Fraud and Abuse Control Program, established by HIPAA, authorizes OIG to provide guidance to prevent fraud and abuse. As part of this mandate, OIG issues Special Advisory Bulletins about industry practices or arrangements that potentially implicate the fraud and abuse authorities subject to enforcement by OIG.

[16] *Id.* at 3.

insured patients.[17] Since that time, OIG and DOJ aggressively have enforced a policy of prohibiting pharmaceutical manufacturers (but not others) from providing any form of copay assistance to federal health care beneficiaries.

114. As OIG has acknowledged, Congress's concern in adopting the AKS and BIS was with providing financial advantages that might steer providers or patients to a particular drug over competitors, or reduce incentives to locate and use less expensive, equally effective drugs, thus reducing the effectiveness or increasing the costs of Medicare. 70 Fed. Reg. 70,623-03, at 70,625 (Nov. 22, 2005). Any analysis of whether a particular program is permissible should, therefore, turn on those criteria. Yet, by imposing a blanket prohibition on manufacturer-funded copay assistance, OIG has drawn an arbitrary line that hinges solely on *who* is providing the financial assistance. Meanwhile, under OIG's guidance, if the person or entity providing financial assistance were a wealthy relative or charity, the subsidy is acceptable. Though OIG has not articulated its reasoning, its endorsement of third-party charitable assistance to Medicare patients makes evident that OIG does not require patients to personally pay the out-of-pocket costs for their prescribed medications. OIG's categorical interpretation of the law barring manufacturers from providing the same assistance to patients fails to recognize the possibility that, in some circumstances—such as that presented by the proposed Programs—a manufacturer's assistance might *improve* health care by allowing patients to access needed medicines that they simply cannot afford, without posing the risks the AKS and BIS were designed to address. In such circumstances, a manufacturer may provide financial assistance to enable Medicare patient access to medicines without falling within the scope of the AKS's and BIS's statutory prohibition.

[17] *Id*.

B. OIG's Restrictions on Pharmaceutical Manufacturer's Interactions with Independent Charities

115. As an alternative to direct copay assistance, OIG has recommended in guidance that manufacturers contribute to *independent* charity patient assistance programs as an avenue to assist financially needy Medicare Part D patients with their out-of-pocket costs. *See* 70 Fed. Reg. 70,623, 70,626-27 (Nov. 22, 2005) OIG noted that "[l]ong-standing OIG guidance makes clear that pharmaceutical manufacturers can effectively contribute to the pharmaceutical safety net by making cash donations to independent, bona fide charitable assistance programs." *Id.* at 70,626.

116. However, OIG has sought to limit even that avenue for assistance. The OIG guidance imposes severe restrictions on a pharmaceutical manufacturer's communications with and donations to independent charities that impede the manufacturer's ability to bestow a meaningful and effective gift by, for example, ensuring the charity has sufficient funds to cover all patients who require assistance accessing treatment or medication. In particular, OIG's 2005 Guidance provides that, "[p]harmaceutical manufacturers should not influence, directly or indirectly, the identification of disease or illness categories, and pharmaceutical manufacturers should limit their earmarked donations . . . that define categories in accordance with widely recognized clinical standards and in a manner that covers a broad spectrum of available products." *Id.* Any discussions between a manufacturer and an independent charity regarding funding levels or patient needs could be considered "attempting to influence," thus violating OIG's broadly worded guidance and creating grounds for the government to assert an AKS or BIS violation. As a consequence, independent charities often structure their funds to cover many products for a number of related disease states, and there is no guarantee that the funds go to patients in need for a particular disease state.

117. Moreover, OIG's 2005 Guidance stated that OIG would look with suspicion on charities focused on a narrow disease category with only one treatment. *Id.* at 70,627. In its 2014 Guidance, OIG further tightened the 2005 Guidance and asserted that charities "with narrowly defined disease funds" may be "subject to scrutiny" if the disease funds "result in funding exclusively or primarily the products of donors or if other facts and circumstances suggest that the disease fund is operated to induce the purchase of donors' products." 79 Fed. Reg. 31,120, 31,121 (May 30, 2014).

118. Following its 2014 Guidance, OIG issued a series of advisory opinions that imposed new conditions on charities that had previously received favorable advisory opinions, requiring the charities to certify that they would not provide help to patients through: (1) single disease funds; or (2) single treatment funds.[18]

119. Both the 2005 and 2014 Guidance acknowledged that, in "rare circumstances," a disease may have only one effective treatment and therefore a disease fund could, in theory, permissibly cover only one manufacturer's product." 70 Fed. Reg. at 70,627 n.19; 79 Fed. Reg. at 31,122. OIG explained, in those "unusual circumstances," the fact that "a disease fund includes only one drug or drugs made by one manufacturer would not, standing alone, be determinative of an anti-kickback statute violation." 70 Fed. Reg. at 70,627 n.19; 79 Fed. Reg. at 31,122. OIG did not further define, however, the circumstances in which such a fund is permissible, presumably leaving entities to seek guidance through the advisory opinion process or to risk enforcement action.

[18] *See, e.g.*, Notice of Modification of OIG Advisory Opinion No. 02-1 (Mar. 03, 2017); Notice of Modification of OIG Advisory Opinion No. 10-07 (May 05, 2016); Notice of Modification of OIG Advisory Opinion No. 04-15 (Dec. 30, 2015).

120. The ambiguity in OIG's guidance on single drug funds makes any charitable copayment support by Pfizer for ATTR-CM patients virtually impossible without judicial clarification of Pfizer's legal rights. Under the government's current enforcement regime, which could result in considerable penalties, independent charities are reluctant to establish a fund for ATTR-CM patients because the Medications are the only FDA-approved drug to treat the condition. Under current OIG guidance, such a fund would be permissible if it also "provided support for other medical needs of patients with the disease," including all prescription medicines to treat symptoms of the disease and side effects of treatment.[19] Still, the practical reality is that OIG has never approved a so-called "single drug fund." Moreover, given that four charities have reached settlements with DOJ related to single drug funds in just the past three years, without assurance that they will not face prosecution, none presently is willing to risk running afoul of OIG's opaque interpretations by establishing a fund for ATTR-CM patients. Pfizer therefore can donate to independent charities that have established funds that cover a number of disease states collectively, including ATTR-CM, but there is no guarantee that these donations would go to ATTR-CM patients in need.

III. Pfizer Faces Imminent Risk of Government Enforcement If It Implements Its Proposed Copay Assistance Programs

121. Notwithstanding OIG's assertion that it would evaluate patient assistance arrangements on a case-by-case basis,[20] DOJ broadly has treated a company's failure to adhere strictly to OIG's guidance on copay and charitable assistance as evidence of intent to violate the AKS or BIS. This determination has serious implications for pharmaceutical manufacturers and

[19] *See, e.g.*, OIG Advisory Opinion No. 10-07 (May 5, 2016).

[20] OIG has stated that "a determination regarding whether a particular arrangement violates the anti-kickback statute requires a case-by-case evaluation of all the relevant facts and circumstances, including the intent of the parties." 70 Fed. Reg. 70,623-03, 70,625 (Nov. 22, 2005).

for patients who rely on financial support from such charitable programs, and it has effectively foreclosed manufacturers from providing direct copay assistance to federal health-care beneficiaries, including Medicare patients.

122. The consequences of an AKS or BIS conviction are Draconian, including the possibility of a pharmaceutical manufacturer's total exclusion from federal reimbursement for its medications. A violation of the AKS or BIS may also serve as a predicate for violation of the False Claims Act, which the government uses to assert a right to collect treble the value of the products implicated, in addition to millions of dollars in statutory penalties. Because of the dire consequences of False Claims Act, AKS, or BIS conviction, unless a pharmaceutical manufacturer can persuade the government not to pursue the matter, it almost always is forced to resolve investigations before they have had any opportunity to test the government's expansive reading of the AKS and BIS in court.

123. In fact, from December 2017 through January 2020, the government collected more than $840 million in settlements with eight pharmaceutical companies (including Pfizer) and $13 million in settlements with four independent charitable foundations, in order to resolve allegations of False Claims Act liability premised on AKS violations in connection with independent charities or direct patient assistance.[21] The government initiated these investigations on the premise that direct copay assistance violates the AKS, and that companies that fail to follow OIG guidance on donations to independent charity foundations are therefore presumptively attempting to pay for patients' copays in violation of the AKS.

[21] Depa't of Justice, U.S. Att'y Office, Dist. of Mass., *Fourth Foundation Resolves Allegations that it Conspired with Pharmaceutical Companies to Pay Kickbacks to Medicare Patients*, (Jan. 21, 2020), https://www.justice.gov/usao-ma/pr/fourth-foundation-resolves-allegations-it-conspired-pharmaceutical-companies-pay.

124. Although OIG has acknowledged the important role that independent charities play in the pharmaceutical payment system, OIG's enforcement posture severely constrains the ability of manufacturers to support those charitable programs to facilitate patients' access to novel treatments, much less to provide financial support directly. The threat of criminal prosecution and other severe penalties in conjunction with an aggressive enforcement posture creates untenable risk for companies to go forward with charitable support activities, even though the companies believe those activities are lawful under the AKS and BIS. The result of this legal uncertainty is reduced funding for and effectiveness of independent charities, which in turn, reduces the support for needy patients to receive prescribed treatments.

A. Pfizer Is at Heightened Risk of Enforcement Because Its Corporate Integrity Agreement Binds It to Follow OIG Guidance

125. On May 22, 2018, in resolution of an investigation of Pfizer's prior contributions to and interactions with independent charities, Pfizer and OIG entered into a Corporate Integrity Agreement ("CIA"), which set forth mutual obligations between Pfizer and OIG. Among other obligations, the CIA requires Pfizer to "comply with all guidance issued by OIG relating to the support and funding of patient assistance programs," including OIG's 2005 and 2014 Guidance.[22] As a result, if OIG's current position that the Proposed Copay Assistance Programs violate the AKS and BIS stands, Pfizer would also be precluded from implementing the Programs under the CIA.[23]

126. The CIA also imposes many restrictions on monetary donations by Pfizer to independent charities and on Pfizer's communications with those charities. For example, Pfizer

[22] HHS OIG, Corporate Integrity Agreement Between the Office of Inspector General of the Department of Health and Human Services and Pfizer Inc., § III(B)(b) (May 23, 2018), https://oig.hhs.gov/fraud/cia/agreements/Pfizer_Inc_05232018.pdf.

[23] The CIA obligates Pfizer to comply with OIG guidance, but does not waive Pfizer's statutory and constitutional rights to petition OIG or the Court for relief from policies that are outside OIG's authority.

may not influence the "identification, delineation, establishment, or modification of, or the parameters relating to" any independent charity's disease fund or its process or criteria for determining eligibility of patients who qualify for its assistance program, may not solicit or use any data or information from an independent charity to correlate the amount or frequency of its donations, and may not provide donations for a disease state fund that covers only a single product or that covers only Pfizer's products.

127. OIG has discretion to determine whether Pfizer has violated the terms of its CIA, and the potential consequences are severe. If OIG were to find that Pfizer violated the CIA, Pfizer could be subject to potentially massive financial penalties, which increase each day that OIG determines Pfizer to be in violation. Critically, if OIG determines that Pfizer has materially breached the CIA, Pfizer could be subject to exclusion from participation in federal health care programs, and "[t]he length of exclusion shall be in OIG's discretion, but not more than five years per material breach." Even a slight risk of these consequences is untenable for any company in the health care industry, let alone a global biopharmaceutical company.

B. OIG's Rejection of Pfizer's Request for A Favorable Advisory Opinion Regarding the Proposed Copay Assistance Programs Puts Pfizer at Heightened Risk of Enforcement

128. As detailed above, Pfizer has attempted to utilize OIG's advisory opinion process to secure approval of the proposed Programs, but to no avail: after a year-long process of engagement with OIG, the agency has refused to issue any opinion with respect to the Independent Charity Program and has informed Pfizer it has rejected the Direct Copay Assistance Program.

129. OIG's unfavorable decision on Pfizer's request for an advisory opinion exposes Pfizer to increased risk of criminal and civil enforcement action from the government if it were to implement the Programs.

130. Without an advisory opinion permitting Pfizer to proceed with the Proposed Copay Programs, Pfizer is bound by OIG's current interpretation of the AKS and BIS, as articulated in its guidance, and cannot proceed with the Programs without threat of enforcement and without potentially violating its CIA.

OIG'S CONSTRUCTION OF THE AKS OR BIS TO PROHIBIT THE PROPOSED COPAY ASSISTANCE PROGRAMS RAISES SERIOUS CONSTITUTIONAL CONCERNS

131. The Proposed Copay Assistance Programs are protected by the First Amendment. The proposed Independent Charity Program would include Pfizer's communications with the independent charity about its preferred charitable goals. An independent charity's communications regarding the creation of a single-drug fund for tafamidis as a way of, among other things, spurring increased charitable giving from Pfizer, is protected activity under the First Amendment.

132. The AKS and BIS already prohibit kickbacks, bribes, and other inducements. OIG's prohibitions on speech incident to charitable giving and solicitation are thus layered on top of these statutory prohibitions, ostensibly as further prophylaxis to prevent circumvention of the statutes. *See McCutcheon v. Fed. Election Comm'n*, 572 U.S. 185, 203 (2014). But as the Supreme Court has repeatedly explained, this "'prophylaxis-upon-prophylaxis approach' requires that we be particularly diligent in scrutinizing the law's fit," because it likely burdens far more speech than can be justified to achieve its legitimate goals. *Id.* at 221 (citation omitted). While OIG's speech restrictions may create clear "rules" about who can say what—and thus ease the burden of proving AKS and BIS violations, thereby also creating another tool for forcing pre-trial settlements—those ancillary benefits do not constitute a compelling government interest. Because that lone benefit is not compelling, no amount of tailoring will suffice and, as a result, the rules imposed by OIG's guidance in this area violate the First Amendment.

133. The speech restrictions are, in any event, overbroad. The communications Pfizer proposes here allow an independent charity to better assist patients and more efficiently meet patient needs. Particularly since ATTR-CM patients have no effective alternative to tafamidis, such communications do not pose a significant risk to any compelling government interest.

134. Notably, Pfizer's efforts to communicate with a charity in order to help that charity assist patients in overcoming access barriers and affording their medications is the same kind of speech that other organizations engage in; the Defendants may not constitutionally single out pharmaceutical manufacturers' speech for restriction.

135. Additionally, the government's interpretation of the AKS and BIS in a manner that significantly hinders access to life-changing medicine for patients with limited financial means, while covering costs for wealthier patients, raises serious equal protection concerns. The purpose of a public insurance program is to ensure that rich and poor alike have access to medical care. Given how the cost-sharing structure of Medicare Part D functions, any construction of the AKS and BIS to prohibit the Proposed Copay Assistance Programs would restrict patients' access to tafamidis solely on the basis of their economic status. In these circumstances, rationing Medicare Part D beneficiaries' access to tafamidis by prohibiting them from benefitting from Pfizer's Proposed Copay Assistance Programs would result in irrational discrimination against middle-income Americans. In the absence of copay assistance, two Medicare beneficiaries—each with the same medically certain diagnosis, each of whom could benefit equally from tafamidis—will have significantly different experiences based on nothing other than their independent financial resources. As a result, the government's actions cannot stand under the Fifth Amendment.

136. The AKS and BIS and the associated regulatory scheme should be construed to permit the Proposed Copay Assistance Programs and avoid these constitutional questions.

COUNT I

Pfizer Is Entitled to a Declaration That the Proposed Copay Assistance Programs Do Not Violate the AKS or BIS

28 U.S.C. § 2201

137. Pfizer incorporates and re-alleges Paragraphs 1–136 as if fully set forth herein.

138. The Declaratory Judgment Act provides that "[i]n a case of actual controversy within its jurisdiction, . . . any court of the United States, upon the filing of an appropriate pleading, may declare the rights and other legal relations of any interested party seeking such declaration." 28 U.S.C. § 2201(a).

139. The AKS and BIS do not prohibit the Proposed Copay Assistance Programs, at least because those programs would not satisfy the remuneration and/or inducement elements of those statutory schemes.

140. An actual controversy or a practicable issue exists between the parties, within the jurisdiction of this Court and involving the rights and liabilities of the parties under the Constitution and laws of the United States, which controversy may be determined by a judgment of this Court.

141. Pfizer is an interested party to the government's actions and is entitled to challenge those actions.

142. Pfizer has exhausted all of its available administrative remedies and/or pursuit of any further administrative remedies would be futile. Pfizer has no adequate remedy at law.

143. Pursuant to Fed. R. Civ. P. 57, the Court "may order a speedy hearing of a declaratory-judgment action." In consideration of the pressing and urgent need for early resolution of this case, Pfizer hereby respectfully requests entry of a judgment in its favor on an expedited basis as provided in Fed. R. Civ. P. 57.

COUNT II

Pfizer Is Entitled to a Declaration That The Application of OIG's Guidance To The Proposed Independent Charity Program Would Violate The First Amendment

28 U.S.C. § 2201

144. Pfizer incorporates and re-alleges Paragraphs 1–143 as if fully set forth herein.

145. The Declaratory Judgment Act provides that "[i]n a case of actual controversy within its jurisdiction, . . . any court of the United States, upon the filing of an appropriate pleading, may declare the rights and other legal relations of any interested party seeking such declaration." 28 U.S.C. § 2201(a).

146. If OIG prevented the Proposed Independent Charity Program, it would infringe on Pfizer's First Amendment right to engage in speech incident to charitable giving and would impose impermissible speaker-based restrictions on Pfizer as a pharmaceutical manufacturer.

147. An actual controversy or a practicable issue exists between the parties, within the jurisdiction of this Court and involving the rights and liabilities of the parties under the Constitution and laws of the United States, which controversy may be determined by a judgment of this Court.

148. Pfizer is an interested party to the government's actions and is entitled to challenge those actions.

149. Pfizer has exhausted all of its available administrative remedies and/or pursuit of any further administrative remedies would be futile. Pfizer has no adequate remedy at law.

150. Pursuant to Fed. R. Civ. P. 57, the Court "may order a speedy hearing of a declaratory-judgment action." In consideration of the pressing and urgent need for early resolution of this case, Pfizer hereby respectfully requests entry of a judgment in its favor on an expedited basis as provided in Fed. R. Civ. P. 57.

COUNT III

Pfizer Is Entitled to a Declaration That The Application of OIG's Guidance To The Proposed Copay Assistance Programs Would Violate The Fifth Amendment

28 U.S.C. § 2201

151. Pfizer incorporates and re-alleges Paragraphs 1–150 as if fully set forth herein.

152. The Declaratory Judgment Act provides that "[i]n a case of actual controversy within its jurisdiction, . . . any court of the United States, upon the filing of an appropriate pleading, may declare the rights and other legal relations of any interested party seeking such declaration." 28 U.S.C. § 2201(a).

153. If OIG prevented the Proposed Copay Assistance Programs, it would discriminate on the basis of wealth without being rationally related to a legitimate government interest.

154. An actual controversy or a practicable issue exists between the parties, within the jurisdiction of this Court and involving the rights and liabilities of the parties under the Constitution and laws of the United States, which controversy may be determined by a judgment of this Court.

155. Pfizer is an interested party to the government's actions and is entitled to challenge those actions.

156. Pfizer has exhausted all of its available administrative remedies and/or pursuit of any further administrative remedies would be futile. Pfizer has no adequate remedy at law.

157. Pursuant to Fed. R. Civ. P. 57, the Court "may order a speedy hearing of a declaratory-judgment action." In consideration of the pressing and urgent need for early resolution of this case, Pfizer hereby respectfully requests entry of a judgment in its favor on an expedited basis as provided in Fed. R. Civ. P. 5.

COUNT IV

The Government's Actions Preventing Pfizer's Proposed Copay Assistance Programs Are Not in Accordance with Law and Contrary to Constitutional Rights under the Administrative Procedure Act

5 U.S.C. § 702

158. Pfizer incorporates and re-alleges Paragraphs 1–157 as if fully set forth herein.

159. The Administrative Procedure Act allows a person suffering a wrong or adversely affected by an agency action to receive judicial review of the agency's action. 5 U.S.C § 702. The reviewing court must set aside an agency's action that is "not in accordance with law" or "contrary to constitutional right." 5 U.S.C. § 706(2)(A) & (B).

160. OIG has engaged in series of actions that establish its position that it is illegal under the AKS and the BIS for Pfizer to implement its proposed Programs to assist ATTR-CM patients through (1) its 2005 and 2014 guidance; (2) its enforcement history; and (3) its refusal to grant Pfizer a favorable advisory opinion.

161. The AKS and BIS do not prohibit the Proposed Copay Assistance Programs because those programs do not meet the remuneration or inducement elements of those statutory schemes. The government's restrictions on pharmaceutical copay assistance generally, and its refusal to provide an advisory opinion affirming that the proposed Programs are not grounds for sanctions under the AKS or BIS, are therefore not in accordance with the law.

162. The government's actions infringe on Pfizer's First Amendment right to engage in speech incident to charitable giving and impose impermissible speaker-based restrictions on Pfizer as a pharmaceutical manufacturer. The government's actions are therefore contrary to a constitutional right.

163. The government's actions discriminate on the basis of wealth without being rationally related to a legitimate government interest. The government's actions are therefore contrary to a constitutional right.

164. In combination with its other actions, OIG's determination that the Proposed Copay Assistance Programs implicate the AKS and BIS is final agency action that prevents Pfizer from lawfully engaging in the Proposed Copay Assistance Programs.

165. Pfizer has exhausted all of its available administrative remedies and/or pursuit of any further administrative remedies would be futile.

166. Pfizer is entitled to challenge the government's actions. 5 U.S.C. §§ 701-706.

167. Pfizer has no adequate remedy at law.

168. Accordingly, Pfizer seeks a judgment setting aside OIG's determination that the Proposed Copay Assistance Programs implicate the AKS or BIS.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff respectfully prays that this Court:

169. Declare that the Proposed Copay Assistance Programs do not violate the AKS or BIS;

170. Declare that the application of OIG's Guidance to the Proposed Copay Assistance Programs would violate the First Amendment to the U.S. Constitution;

171. Declare that the application of OIG's Guidance to the Proposed Copay Assistance Programs would violate the Fifth Amendment to the U.S. Constitution;

172. Set aside OIG's determination that the Proposed Copay Assistance Programs implicate the AKS and BIS as not in accordance with law and contrary to a constitutional right;

173. Award Plaintiff such costs and reasonable attorney's fees to which it might be entitled by law; and

174. Award such other relief as this Court may deem just and proper.

Dated: June 26, 2020

Respectfully submitted,

/s/ Joan McPhee

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